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LECTURES ON THE HERTER FOUNDATION.*

By Professor Albrecht Kossel,

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The Proteins.

The history of physiology shows that chemistry has rendered very varied services to the former science during the different periods of its development. If we consider the history of physiology and chemistry during the Eighteenth and Nineteenth centuries, we see that organic chemistry has been gradually evolved from the study of substances of physiological importance. The simplest of the many substances produced by living organisms were isolated and systematized. From the study of these compounds a knowledge was obtained of the chemistry of carbon and of its manifold combinations with hydrogen, oxygen, nitrogen and other elements, such as could not have been derived from a study of inanimate nature. The theories of structural chemistry based upon the investigations of these substances have in turn resulted in the development of synthetic chemistry. For some time structural chemistry was busily engaged with the completion of this system and every effort was directed towards the rapid development of chemical technique. During this period pure chemistry was less intimately in touch with physiological problems. Both sciences, physiology and chemistry, seemed to drift further apart. The former devoted itself more especially to synthetic work, while the latter concerned itself principally with mechanical and physical questions and conceptions. The conviction that a comprehensive understanding of the substances taking part in vital processes was one of the most important tasks of structural chemistry was never quite extinct, but for a time no active steps were taken for its acquisition.

A new period began with the investigations upon the constitution of uric acid and other purine derivatives, upon the behavior of aromatic substances in the animal organism, and with the development of the chemistry of the carbohydrates. Theoretical chemistry began to exercise a new and powerful influence upon physiological conceptions. The growth of this influence has been due in part to the interest which theoretical chemistry has taken in determining the physical laws governing ferment action, but more especially because of the investigations upon proteins undertaken by certain prominent organic chemists.

The investigation of the chemical nature of the protein substances has made considerable strides in the two last decades and has had a corresponding influence upon physiological questions. I now propose to give a short account of the state of our knowledge in this field of work.

The development of the chemistry of the proteins has been very irregular; at times no progress appeared to be made at all and then suddenly renewed activity would result from fresh inspiration. The older investigators had already succeeded in separating certain definite chemical individuals from the mixture of substances resulting from the hydrolysis of proteins and the number of these isolated compounds increased as time went on. It was inferred that the molecular structure of the proteins was very complicated since the products of hydrolysis were so numerous and varied. The problem as to

* Delivered in the Medical Department of Johns Hopkins University, October, 1911.

how these simpler derivatives were arranged in the original protein molecule appeared to be very difficult of solution, and prior to the 90's but few investigators seriously concerned themselves with this question.

Paul Schutzenberger was the only investigator who attacked the problem with any breadth of view. His experiments, which were made during the 70's, were essentially similar in aim with those of more recent times, but his deductions were not sufficiently convincing to arouse general scientific interest nor to stimulate further work along these difficult lines of investigation.

Gradually it came to be recognized that essentially there were three separate fundamental problems which awaited solution. First, that of the composition and constitution of the fragments or products of hydrolysis; second, that of the relative proportions of these substances; and finally, that of the mode of combination and arrangement of these fragments in the protein molecule.

Knowledge of the individual fragments of the proteins is most important, since in animal metabolism we are dealing with them as reacting units. Our aim is to determine their structure and their physiological relationships. The determination of their structure is often as important as the solution of physiological questions. For chemical structure based on spatial relationships gives information about the mutual relations of the individual atomic groups, many of which are combined in the larger molecules. It indicates how a particular substance will react under given conditions and what chemical transformations it may undergo. A clear understanding of the structure of the constituents of living organisms and of their food-materials is the first step towards a knowledge of biochemical processes.

Investigation of the fragments obtained by the decomposition of protein substances has shown that the protein molecule is made up of a collection of units which in German are called *Bausteine*, or building-stones. These *Bausteine* are represented by the decomposition products which are obtained by hydrolyzing proteins by means of acids, alkalies, or by the action of enzymes. The *Bausteine* which are found in a single protein are of various kinds, but they nearly all have something in common. Most of them are characterized as α-amino-acids.

TABLE I.

CH_2NH_2	CH_3	CH_2OH	CH_2SH
COOH	$CHNH_2$	$CHNH_2$	$CHNH_2$
	COOH	COOH	COOH
Glycocoll	Alanine	Serine	Cysteine
$CH_2C_6H_5$	$CH_2C_6H_4OH$	$CH_2C_8H_6N$	$CH_2C_3H_3N_2$
$CHNH_2$	$CHNH_2$	$CHNH_2$	$CHNH_2$
COOH	COOH	COOH	COOH
Phenylalanine	Tyrosine	Tryptophane	Histidine

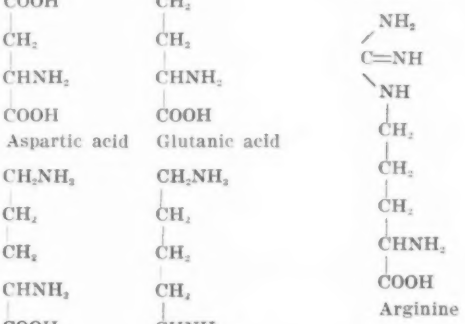
Glycocoll may be considered as derived from acetic acid by the substitution of one hydrogen atom by the group NH_2; alanine may be regarded as derived from glycocoll by the substitution of one hydrogen atom by the CH_3 group, while the further substitution of a hydrogen atom in alanine by the phenyl group gives us phenylalanine. If instead of the phenyl group we substitute the heterocyclic indol radical, we obtain indolalanine or tryptophane, while if we choose as substitutent a hydroxy-phenyl group, an oxygen atom, or a sulphur atom, we obtain respectively tyrosine, serine and cysteine.

If we consider these compounds as derived from glycocoll by the substitution of different organic groups, we see that the character of the molecule may be modified in two ways: First, by the introduction of acid groups we may obtain substances with pronounced acid characteristics, such as aspartic and glutamic acids; secondly, by the introduction of basic groups we obtain substances with strongly basic properties, such as we observe in the substances histidine, ornithine and lysine.

TABLE II.

COOH	COOH
CH_2	CH_2
$CHNH_2$	$CHNH_2$
COOH	COOH
Aspartic acid	Glutanic acid
CH_2NH_2	CH_2NH_2
CH_2	CH_2
CH_2	CH_2
$CHNH_2$	CH_2
COOH	$CHNH_2$
	COOH
Ornithine	Lysine

TABLE III.

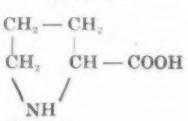


Arginine

In addition to these amino-acids we find in the protein molecule a radical of quite different character, containing one carbon and two nitrogen atoms. It is always found in combination with ornithine (diaminovaleric acid). The compound produced by the union of the amidine group with ornithine is known as arginine.

Proline, a substance with a peculiar cyclic structure, together with oxy-proline, forms a separate group. Both of these substances are derivatives of pyrrolidine.

TABLE IV.



Proline

It is very probable that atomic groups are present in the protein molecule which have up to the present evaded detection. It is unlikely, however, that these substances are of much quantitative importance. It is true that the structure of one product of protein hydrolysis, diaminotrioxydodecoic acid, with the empyrical formula $C_{12}H_{26}N_2O_5$ has still to be elucidated.

The complexes which are formed by the union of these various atomic groups or *Bausteine* are known as the albumins or proteins. These proteins may contain either few or many of these constituent groups. Thus we know proteins which yield not more than five of these groups while others yield all of them. Where the succession of carbon atoms is interrupted by the presence of other atoms it is usually found that the molecule will undergo disruption at this point, either within the living organism or without.

We find that there are some proteins which fail to yield certain cleavage products, while in some other cases we encounter cleavage products which are so exceptional that we are not justified in considering them as typical protein derivatives. Glucosamine, an amino derivative of glucose, is a case in point.

The quantitative relations of the cleavage products derived from any particular protein are believed to be constant. The following table indicates clearly that different proteins yield widely different amounts of the various cleavage products. It is possible to estimate these cleavage products with accuracy only in the case of a few of them. In most cases the figures in the table represent the yield of substance capable of separation rather than the amount actually present, which naturally must be somewhat greater. However, the results are amply sufficient to indicate the wide differences in composition of different proteins.

TABLE V.

THE FIGURES INDICATE THE YIELD OF THE CLEAVAGE PRODUCT IN GM. FROM 100 GM. OF THE PROTEIN.

	Casein (Osborne and Guest).	Wheat gliadin (Osborne and Guest).	Silk fibroin (E. Fischer and A. Skita).	Histone (Kossel, Kutscher, Abderhalden, Rona).	Sturine (Kossel, Weiss, Dakin).	Salmine (Kossel and Dakin).
Glycocoll	0	0	36	0.5	....	0
Alanine	1.50	2.00	21	3.46	pres.	0
Valine	7.20	3.34	....	....	0	4.3
Leucine	9.35	6.62	1.5	11.8	pres.	0
Proline	6.70	13.22	(0.3)	1.46	0	11.0
Phenylalanine	3.20	2.35	1.5	2.2	....	0
Glutaminic acid	15.55	43.66	....	3.66	....	0
Aspartic acid	1.39	0.58	pres.	....	....	0
Cystine	?	0.45	....	....	0	0
Serine	0.50	0.13	1.6	....	0	7.8
Tyrosine	4.50	1.20	10.0	6.31	0	0
Oxyproline	0.23	....	...	....	....	....
Histidine	2.50	0.61	....	1.21	10.3	0
Arginine	3.81	3.16	1.0	14.36	57.9	87.4
Lysine	5.95	0	....	7.7	7.9	0
Tryptophane	1.50	[1.00]	....	....	0	0
Diaminotrioxydodecoic acid	0.75	....	....	....	....	....
Ammonia	1.61	5.22	....	1.66	0	0

These results force us to the conclusion that the chemical structure of proteins with varying properties possess entirely different structures. We must also conclude that the atomic groupings of the various cleavage products actually exist as such in the protein molecule; for on hydrolysis of the same protein they are always obtained in constant quantity. It is improbable that complicated intramolecular changes accompany their formation, for they are obtained from proteins not only by chemical reactions at high temperatures, but also at body temperature by the action of enzymes.

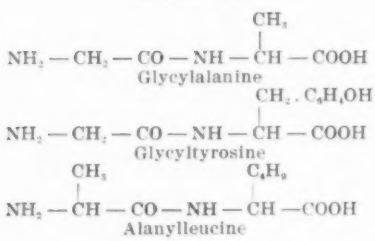
The conception of the proteins as substances formed by the union of simple cleavage products indicates a certain resemblance between them and the carbohydrates. The complex carbohydrates which are stored in the tissues, *i. e.*, the polysaccharides, are similarly derived from the union of groups containing five or six carbon atoms which are analogous to the cleavage products of the proteins. These groups are united with each other by means of oxygen atoms and may be readily separated by means of the hydrolyzing action of acids or enzymes. The large organic molecules which are built up as the result of the activities of living cells are thus seen to possess a certain similarity as regards their component parts. They are to a certain extent formed by the loose union of simple groups in such a way that they may easily undergo change and rearrangement in the course of the metabolic changes occurring in the living body.

This relationship is also recognizable in the case of the fats. The cleavage products are in part larger, for they include molecules containing 16, 18 or even more carbon atoms arranged in a straight chain. The cyclic structures present in related substances, such as chlosterine, play a less active rôle, presumably because these continuous carbon groups are less easily decomposed by the living organism.

The recognition of the fact that the proteins, like the polysaccharides, are made up of simpler derivatives, leads us to consider the question as to how these derivatives are united with one another. I first began my investigations on the protamines with the hope of obtaining a solution of the constitution of these simple protein substances, and came to the conclusion that the union of the *Bausteine* was effected by means of the imid groups. Emil Fischer, through a series of masterly investigations, has definitely shown that this type of combination is found in all protein substances.

We can distinguish two forms of this imid combination. The one is produced by the union of a carboxyl group with an amido group, with elimination of the elements of water. In this case a carbonyl group is adjacent to the imido group . . . CO−NH−C . . . The second form is produced by the union of an amino group with urea, water being eliminated in this case also. In this way a guanidine grouping is produced: $NH_2-CNH-NH-C$ . . . Th. Curtius, and especially Emil Fischer, have shown by their synthetic experiments that it is possible to combine the cleavage products of the proteins according to the first form and to obtain substances which in their properties closely resemble the more complex protein derivatives. Furthermore Fischer and his co-workers have actually succeeded in separating from proteins derivatives which yield on hydrolysis only two to four cleavage products. It has thus been possible to make a comparison between the synthetic products and similar substances derived by the hydrolysis of proteins and so to place the constitution of the latter on a firm basis. The following formulæ give certain examples of polypeptides obtained from proteins.

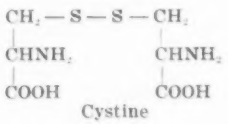
TABLE VI.


CH3
NH2 — CH2 — CO — NH — CH — COOH
Glycylalanine
CH2 . C6H4OH
NH2 — CH2 — CO — NH — CH — COOH
Glycyltyrosine
CH3 C4H9
NH2 — CH — CO — NH — CH — COOH
Alanylleucine

The second type of imid combination was recognized by E. Schultze and was confirmed later by synthesis. Its resolution takes place under different conditions from those affecting the first type. It is more resistent to hydrolysis by means of dilute acids and only undergoes cleavage when subjected to the action of a specific ferment.

The imid form of combination is not the only one effecting the union of carbon groups in the protein molecule. Baumann's determination of the constitution of cystine, which has since required but slight modification, was made in the 80's. He found that this cleavage product consisted of two carbon groups united by means of a sulphide linkage. The resolution of this linkage is effected by reduction and not, as in the other cases, by hydrolysis.

TABLE VII.



Let me illustrate the complexity of the constitution of the proteins by a few examples. First of all I should like to draw your attention to a group of proteins called *protamines*. In my opinion these substances are of great importance and I have been engaged upon the investigation of them for some time.

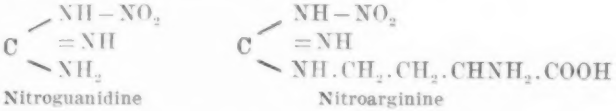
The protamines are distinguished from other proteins by two peculiarities: one is that they have a simpler constitution than any other proteins with which we are at present acquainted; the other is that they possess strongly basic characteristics. The protamines form a group possessing a very limited distribution. Up to the present they have only been found in the spermatozoa contained in the testicle of certain fish. We can distinguish various types of protamines and the group is connected with the more complex or "higher" proteins by means of substances of intermediate complexity.

The most varied protein constituents take part in the formation of the protamines: the mono-amino-acids, including alanine, serine, tryptophane, tyrosine, amino-valeric acid, amino-caproic acid and proline—the di-amino-acids, including ornithine and lysine, also histidine. In union with ornithine we find the "urea-forming" group, the whole forming arginine. All of these groups are not formed in the same protamine molecule; indeed the protamines represent combinations containing a few of these groups.

The simplest variety of protamine I may call the salmine type. This type predominates in protamines which are obtained from the testicles of mackerel, herring, pike, and salmon. Salmine, which was isolated by Miescher and called "protamine," was the first of these substances to be discovered. It belongs to the class just mentioned, together with clupeine, esocine and scombrine. In a second class of protamines we place cyclopterine from Cyclopterus Lumpus and one of the protamines obtained from the testicles of the carp, namely, β-cyprinine, and possibly also crenilabrine from Cr. Pavo. In a third class of protamines we have only one representative, namely α-cyprinine. Sturine, a protamine derived from the testicles of the sturgeon, belongs to a fourth class.

The relationships between the members of the first class are simplest. These substances on hydrolysis yield a large quantity of arginine as well as various amino-acids; alanine, amino-valeric acid, serine and proline. The quantitative relations are such that upon hydrolysis 8/9 of the total nitrogen is found in the form of arginine. Since arginine contains four atoms of nitrogen, we infer that in these protamines there is one molecule of mono-amino-acid for every two molecules of arginine. Judging by experience and by our present knowledge of the mode of union of various groups we are forced to conclude that at least two arginine groups are united together. Hence di-arginide or poly-arginide groups are present in the molecules of these protamines. Certain observations, the details of which I cannot at present enter upon, indicate that these protamine molecules are composed of di-arginyl-alanine, di-arginyl-serine, di-arginyl-proline, di-arginyl-amino-valeric acid, etc., and the results of the analysis of the hydrolytic cleavage products confirms this assumption. The union of these various *Bausteine* is effected in such a manner that the strongly basic groups are still free. Goto's experiments upon the capacity of clupeine to combine with acids showed that each arginine molecule corresponds to one alkali equivalent.

Recently with E. L. Kennaway and A. T. Cameron I have made additional observations which also show that one of the amido-groups in the arginine contained in the clupeine molecule must be free and able to react. It is for instance not difficult to introduce a nitro-group into clupeine and on hydrolysis of the nitro-clupeine, nitro-arginine is found among the cleavage products. Nitro-arginine is a substance which apparently must be regarded as a derivative of the asymmetric nitro-guanidine described by Thiele:



From these results and from experiments on the action of nitrous acid on protamines we infer that it is the amino-group in the arginine contained in the molecule of the protamines of the salmine group which is responsible for the basic properties of the whole molecule. In the protamines of other classes different groups may influence the basicity of the molecule. Thus Hirayama and Pauly have shown that the iminazol ring present in the histidine contained in sturine is free and is not

bound in peptide fashion. The same is true of the amino-groups of the lysine present in α-cyprinine—a simple protamine containing but little arginine. Also the lysine contained in sturine has one or two free amino groups.

While some of the amino-groups of the protamines are free, and are not linked with other *Bausteine*, the carboxyl groups on the other hand are mostly combined. This follows from Goto's observations on the diminishing alkalinity of clupeine upon hydrolysis. This is apparently due to the resolution of ester-like groupings, containing serine.

The application of these various observations and deductions to the protamines shows clearly that the examination of these simple proteins is capable of indicating the lines of investigation which will be helpful in determining the composition of the more complex ones. The propriety of grouping together the protamines and the more complex proteins, which in the past has sometimes been questioned, cannot now be doubted. Many facts indicate this most clearly—not the least important being the discovery of proteins intermediate in complexity between the protamines and the more complicated proteins.

In *typical* proteins the mono-amino-acid groupings are so much increased in quantity and complexity that they are of paramount importance. In certain kinds of typical proteins, however, the basic properties, dependent upon the presence of free amino-groups are very well marked. This is the case with the proteins known as *histones*. The cleavage products of the histones are very rich in basic di-amino-acids, although to a lesser extent than those of the protamines. While in the protamines almost 89 per cent of the total nitrogen appears in the form of arginine, the histones yield about 27 per cent in this form; this is however more than one finds in most typical proteins. But there are certain other proteins which contain just as much arginine without possessing the properties of the histones. The peculiarity of histones consists not so much in the presence of a certain number of basic substances among the cleavage products, but rather in the presence of *free basic* groups in the histone molecule itself. In addition the histones have a few other peculiarities in common with the protamines, such as the property of uniting with other proteins to form sparingly soluble precipitates. Their physiological relations also point to resemblances with the protamines; especially the fact that they appear in combination with nucleic acids as constituents of the cell-nucleus.

The more complicated proteins exhibit great differences among themselves, for they vary not only according to their physiological relationships, but also according to the conditions of their formation and the functions they subserve in the living organism. I have already indicated how a complex protein may lack one or another of the *Bausteine* and how in other cases one or another may predominate. I should like to draw your attention to a few examples of this kind.

A striking example was found by Kutscher and myself in our work upon the distribution of lysine. We found that this *Baustein* which is so commonly present in most proteins was entirely absent from a vegetable protein characterized by its solubility in alcohol. From the later investigations of Hopkins, Osborne and Abderhalden it was found that the tryptophane and glycocoll groupings were also absent from the same protein. The systematic examination of the cleavage products of thoroughly typical proteins such as egg-albumin, casein and serum albumin has also demonstrated the absence of glycocoll. Many proteins fail to yield cystine and tyrosine. On the other hand no substance of protein character has ever been found which did not contain the arginine grouping.

In the early stages of the development of protein chemistry it was found necessary to distinguish two kinds of proteins—"the true proteins" and "the albuminoids." This distinction was made partly upon chemical grounds and partly for physiological reasons. The true proteins were supposed to contain all the essential constituents of the protein molecule while albuminoids, on the other hand, lacked some of the typical *Bausteine*. The former were regarded as of full nutritive value while the latter were not. But some proteins were classified as albuminoids which did not lack any of the typical cleavage products, but which for some other reason, such as difficult solubility, could not take part in the metabolism of some species of animals. Keratine is an example of this kind. The so-called true proteins were, however, regarded as of equal value from a metabolic point of view. Such a classification as this can no longer be maintained and the theory of albuminoids must be abandoned. The construction of a system for the classification of constituents of the living body based upon a mixture of chemical and physiological criteria was bound inevitably to lead to confusion. If today we relegated to one group gelatine, elastine, the proteins of silk and perhaps the protamines as well, we should obtain a class of proteins which could only be characterized by the fact that the individual members had nothing in common with each other.

The complexity of structure possessed by the proteins is much increased by the fact that the molecules which already are very large, readily combine with each other or with other substances. This is readily seen, for example, when protamines combine with the proteins—a precipitate being formed at once on mixing feebly alkaline solutions of the two components. The combination of histones with other proteins may be observed in the same way. It is not unlikely that similar compounds are formed when, in the course of chemical analysis, animal tissues are brought in contact with aqueous solutions. It is probable, moreover, that conditions exist in the animal organism which permit of the formation of these compounds. Hoppe-Seyler suggested the name "proteide" for these complex substances consisting of a protein in combination with an additional substance called later a "prosthetic" group.

In the class of proteides we must include the blood colouring matters, mucoids, nucleins and many other tissue constituents. Our knowledge of these substances is but slightly developed, but we are already aware of their great complexity due to the variety of added prosthetic groups.

The simplest members of this group are those in which iodine, iron or some other element is combined with the protein molecule. Protein complexes containing iodine are found in invertebrate marine animals and also in the thyroid gland.

In the first of these cases Wheeler, Jamieson and Mendel have shown that the iodine is combined with the tyrosine complex, for on hydrolysis the iodine containing protein yields di-iodotyrosine.

In hæmoglobin we find complex organic groups united with the proteins. These groups are themselves colored and the color of hæmoglobin itself is due to them. Chemical investigations have shown that the prosthetic group of hæmoglobin is a complex containing 34 carbon atoms containing several pyrrol rings and also iron in organic combination.

The nucleins, which are characteristic constituents of cell nuclei, contain as the prosthetic group the so-called nucleic acid, which is also very rich in heterocyclic rings. In addition it contains other remarkable groups. I found as constituents of nucleic acids a number of organic substances which are now grouped together under the name of purine derivatives, including adenine, guanine and their derivatives, hypoxanthine and xanthine. I also found the pyrimidine derivatives thymine and cytosine and in addition an atomic complex which must be regarded as belonging to the carbohydrate group. This complex group of molecules is also combined with phosphoric acid, the elements of water being eliminated. Nuclein is formed by the union of this complex nucleic acid with protein. The proteide nuclein may be obtained artificially by bringing together solutions of the two components when nuclein immediately separates out as a precipitate.

A prosthetic group closely resembling nucleic acid is found in guanylic acid derived from the pancreatic gland. The composition of guanylic acid is similar to but simpler than the nucleic acid previously mentioned. Besides these we know of the existence of yet another series of phosphorus containing proteides, but the nature of their prosthetic group is still quite unknown.

Reactions entirely similar to those of the nucleic acids may also be observed in the case of chondroitic acid which is found most abundantly in tissues such as cartilage. Like nucleic acid, chondroitic acid combines directly in aqueous solution with proteins to form a proteide insoluble in water. Some of these artificially prepared proteides are readily resolved into their components, as is the case with salt-like combinations. The protamine present in the substances formed by its union with more complex proteines may readily be recovered on subjecting the compound to peptic digestion. Under these conditions the more complex proteide undergoes hydrolysis while the protamine resists the action of the pepsin and may be separated by the use of suitable precipitants. On the other hand there are other proteides in which the prosthetic group is so firmly bound to the protein that vigorous chemical methods must be employed to effect their separation. Under these conditions one obtains a complex mixture of cleavage products, from both prosthetic group and protein, the separation of which presents great practical difficulties.

On this account it has proved impossible to separate with certainty the intact prosthetic group from many mucoids and phospho-proteins.

F. von Muller and Lanetti have shown that a glucosamine group is present in many mucines and mucoids and, indeed, the distribution of this carbohydrate group has proved to be so wide that many authors are inclined to include it among the typical protein cleavage products.

These chemical investigations which I have briefly put before you today raise the question as to whether the different protein substances which we have been able to separate from animal or vegetable tissues, owing to their varying chemical characteristics are really to be regarded strictly as chemical individuals. Are our criteria which we employ for judging of the purity of these substances in their preparation and purification sufficiently stringent?

We must admit that the larger and more complicated the molecule the more readily certain differences in composition escape one's attention. Thus, the large atomic complex made up of many similar groups, such as we find in the proteins, might undergo substitution of one group for a similar one with so little effect upon the properties of the protein that they might evade detection. We must also admit a certain variation in the constitution of proteins analogous to the small variations which we observe in different organized structures. It is probable, therefore, that the proteins which we may separate from animal organs are not always chemical individuals in the strict sense of the word. Many small analytical variations may be ascribed to this cause.

These considerations do not, however, seriously detract from the value of investigations in the field of protein chemistry. If we consider our analyses as applying to representatives of certain types of proteins rather than to chemical individuals in all cases there can be little doubt that we shall be able to profitably speculate as to the general laws governing the building up of proteins from their simple cleavage products.

The results which have already been obtained have been sufficient to stimulate the study of metabolic problems and to present many new points of view. I shall hope to show you this in my next lecture.

II.

We must infer from the constant occurrence of the proteins that the phenomena of living matter are dependent upon the presence of these substances. But we know very little of the significance of the proteins in connection with the manifestations of life. It is clear that their rôle is a complex one. They fulfill a part of their function while, in the form of complete molecules, they take part in the vital processes. Another part of their functions concerns their ability to act as receivers of substances for synthetic purposes, for the taking up from time to time of substances of low molecular weight, the more readily transportable atomic groups, and the storing of the energy contained in them.

The functions of the proteins are in part dependent upon their physical characteristics, in part upon their chemical properties. In many cases we encounter them taking part in the formation of tissues of definite form and shape, in the same way as cellulose is formed among plants and chitin among the invertebrates. We see how their physical properties are made

use of in the resistance of keratin, the elasticity of elastin, the transparency of the refractive part of the eye.

We all know how easily the proteins react with mild chemical reagents, how readily they are altered by acids and alkalies and the ease with which they yield compounds, metallic oxides, acids and other substances. Some of these derivatives are often encountered in the tissues and secretions. The fact that proteins are so prone to undergo chemical change is to be referred to the presence of carboxyl, amido and imido groups, the occurrence of these groups in many proteins being definitely proved. I have already mentioned that in some proteins the basic properties predominate, in others, the acid; the former is the case with the protamines and histones while casein and similar proteins belong to the latter group. These properties must also assert themselves in the living cell, although we must admit that we know nothing of how this takes place. We must assume that the chemical changes that are concerned in the formation of new organic parts, with the production of "immune substances" or similar bodies and with the acceptance and transmission of stimuli, cannot take place independently of the proteins, but we are at present unable to formulate any picture of the chemical mechanism of these processes.

One might imagine that a comparison of the chemical structures of the proteins with their occurrence in the organism would shed light upon these and similar problems. The results of such researches, however, are but few, since the methods of investigation are primitive. Notwithstanding this, I believe that one may draw some very noteworthy conclusions from series of observations upon young cells especially rich in nuclei. In the growing animal we invariably observe a storing up of nitrogen. This nitrogen in the proteins is partly in the form of arginine, partly also as lysine and histidine, and in addition we find a large quantity of nitrogen-rich substances in the prosthetic groups of the nuclein substances. This is especially characteristic of those portions of the body substance which are concerned with reproduction and growth.

On the other hand we observe that when protein substances have been elaborated for purely mechanical functions they are commonly deficient in basic constituents. This is the case with elastin and with silk-fibroin, for in these protein molecules the monamino acid groupings predominate to such an extent that the nitrogen-rich groupings seem to be almost absent. These results clearly indicate how investigations upon the structure of the proteins can yield results having a direct bearing upon the problems concerning plasma and cells. The development of protein chemistry has, however, proved of greater value in the study of metabolic processes than in any of the other branches of physiology.

In my last lecture I have drawn attention to a property shared by the proteins with the other substances of high molecular weight present in the organism. This consists in the numerous atomic complexes linked together by means of oxygen atoms or NH groups, and I have already indicated that these complexes are readily set free during metabolic changes and subsequently reunited. These changes also take place in the process of transportation of these large molecules. The proteolytic ferments are the agents used by the organism for the breaking down of the proteins into their *Bausteine*. They attack the proteins in much the same way as *oxylytic* ferments attack complex carbohydrates. In the latter case disruption occurs at the point where hexose or pentose groups are linked by means of an oxygen atom, while in the case of the proteins scission takes place at the point where the various groups are united by NH linkages. The action of the different *iminolytic* ferments may be more or less far-reaching. Thus the disintegration of the protein molecule may yield complex products of high molecular weight, such as the albumoses and peptones—this is known to be the case in peptic digestion. Other ferments are unable to attack the unaltered proteins, but are able to act upon their decomposition products. From investigations made upon the behavior of polypeptides it has been found that their constitution and configuration determine whether they are attacked by proteolytic ferments or not. The behavior of arginine, a substance derived from the union of ornithine with a urea-forming group, is especially noteworthy. It is unattacked by hydrolysis with acids and with most active ferments, but is readily decomposed by a specific ferment, arginase, which is found in certain organs of animals and plants.

The activation of these ferments takes place either inside or outside the living cell at definite times according to the needs of the organism. What are the conditions which determine these needs of the organism? Is the breaking down of the larger molecules simply for the purpose of facilitating their transport? Or is the breaking down of the proteins by means of enzymes into their components merely the first step toward their complete decomposition?

The point of view necessary for the proper consideration of these problems has only been obtainable since the newer development of protein chemistry. So long as we were unaware of the great difference existing between individual proteins it was impossible to understand why protein food should be decomposed before being converted into body protein. The demonstration of such a far-reaching decomposition of proteins in the intestinal tract of higher animals follows from several observations, of which I shall refer to one only. Szumowski made the following experiment in my laboratory: He fed geese with corn (maize), until they had materially increased in weight, *i. e.* they had stored up nutrient material. He then killed the animals and examined the organs for the presence of the peculiar protein of corn—the so-called zein. This examination was the more easy since zein is completely different from the animal proteins. Its ready solubility in alcohol serves for its separation from the proteins present in animal organs, and, in addition, zein is characterized by the absence of the lysine group. When the administration of zein was by way of the alimentary canal, *i. e.* the natural method, this protein was never detected in the organs of the geese. When, on the other hand, the zein was introduced into the circulation directly, it was possible to demonstrate its accumulation in the liver. This experiment leads us to the conclusion that in the herbivorous animal a rearrangement of the food proteins must take place so that from the lysine-free zein we

obtain the differently constituted animal protein. Similar transformations must take place in plant seedlings when the protein constituents of the young plant are formed from the proteins of the endosperm, or similarly in the case of the chick in its development at the expense of its albumin reserves. In the latter case all the different proteins found in the blood, nervous system, connective tissue, and muscle are formed from the proteins of the yolk and white of egg. In the same way the keratin of the feathers, the gelatin yielding substances, or the globin of the red-blood cells, must be formed from the same mixture of food proteins. The composition of these various proteins is so different that their formation must be preceded by a breaking down of the chemical structure of the food protein before reconstruction with new protein is possible. Similar rearrangements must take place in every growing organism and are especially prominent in those cases in which one organ is developed at the expense of another whether under normal or pathological conditions. From investigations by Wakeman we must conclude that in phosphorus poisoning the tissues become poorer in arginine, hence it is probable that proteins poor in arginine are formed. The opposite change is seen in the formation of the male sexual products. The Rhine salmon is particularly well adapted for demonstrating this change. This fish takes no nourishment during the time of the ripening of the testicles, and takes the protein material for the formation of sperms from its own body, especially from the muscles. In this way from the arginine-poor proteins of the muscles is obtained the arginine-rich and completely differently constituted protein making up the head of the sperm. This protein belongs to the class of protamines. The diminution in muscle substance has been quantitatively determined by Miescher and in my laboratory Weiss has carried the investigation a step further by determining the distribution of arginine during the process. It was found that the amount of arginine originally present in the muscle before wasting is sufficient to cover the arginine requirements of the growing testicles. It is therefore unnecessary to assume that this protein constituent is specially synthesized during the ripening of the testicle. It appears more probable that the constituents derived from the decomposition of the muscle protein are utilized for the formation of the new protein. The greater part of the mono-amino acids of the muscle protein do not appear in the protamine molecules; apparently they are utilized during the period of testicle formation for the nourishment of the rest of the body while the nitrogen-rich part is used for the formation of the new protein. These changes which accompany the ripening process differ somewhat among the various families of fishes. In all cases basic groups predominate in the newly formed molecules. A larger or smaller amount of arginine is invariably present, but the atomic groups other than arginine vary widely, as I have already mentioned in my first lecture. These rearrangements presuppose a prior decomposition, but we have no knowledge as to how far the original molecule undergoes disintegration. It is possible that the molecule is completely resolved or it may be that decomposition takes place to only a limited extent. The same problem presents itself in the consideration of the formation of other proteins, as we shall see in a moment.

In the foregoing discussion we have been considering the proteolytic changes in the animal organism and we have seen that the decomposition of protein molecules in the animal body may take place by the action of hydrolytic ferments, the elements of water being taken up. From what has gone before, it is also clear that the living organism has the power to bring about the reverse process, namely the reunion of these products by hydrolysis with elimination of water.

Physiological chemists have long known that the amino group of glycocoll is capable of union with a carboxyl group through biochemical action. The formation of hippuric acid by the union of the amino group of glycocoll with the carboxyl group of benzoic acid is an example of this. In the same way the organism of the bird effects the union of another protein derivative, namely ornithine with benzoic acid. These changes are analogous to the formation of proteins from their cleavage products. Notwithstanding this, however, the conception of a synthesis of protein in the animal body was not entertained by those of the older physiologists interested in the problems of metabolism. It was generally held that the proteins partly unchanged and partly in the form of albumoses and peptones, were absorbed from the products of digestion, and that the portion of the proteins which underwent hydrolysis by means of the digestive ferments could no longer serve for synthetic purposes. It was observed that albumoses and peptones disappeared when brought in contact with intestinal mucous membrane. This was assumed to be due to their being taken up by the intestine in the same way as in normal absorption. The albumoses and peptones were assumed to be bound by union with the histological elements of the mucous membrane. The observations of Kutscher and of Cohnheim necessitated a modification of these views. Kutscher showed that the decomposition processes occurring in the intestines were much more far reaching than had been previously supposed, while Cohnheim showed that the disappearance of peptone when brought in contact with intestinal mucous membrane was not due to its absorption, but rather to its decomposition. A ferment called erepsin is present in the mucous membrane which is able to effect the complete decomposition of peptone into its *Bausteine*. These *Bausteine* rapidly disappear on absorption since they cannot be detected in the blood.

A series of experiments to determine the question of the regeneration of protein in the living body were begun about this time. The cleavage products of proteins were fed to animals and observations upon the nitrogen balance were then made. Is it possible to bring about an increase in body protein as the result of the feeding of these protein *Bausteine?* If this could be demonstrated, the power of the animal body to effect protein synthesis would be proven.

The first experiments of this kind were successfully carried out by O. Loewi. He fed a dog with the products of autolysis of pancreatic tissue containing all the protein cleavage products, with a resulting increase in body protein. These experiments have been frequently repeated and modified and there

is now no question of the formation of new protein in the animal body from completely hydrolyzed protein cleavage products *i. e.* from its *Bausteine*. The experimental method required considerable development and especial efforts were made to obtain a preparation which on the one hand contained all the *Bausteine* of protein, and on the other hand was *completely* hydrolyzed. Convincing proof of the correctness of Loewi's conclusions was given by Abderhalden and his co-workers. Meat subjected to the action of various proteolytic ferments was used as starting material. It was soon found that the disappearance of the biuret reaction was no certain indication of complete hydrolysis, polypeptides being formed which do not give the biuret reaction. Sörensen's method of formaldehyde titration was used successfully for determining the point of complete hydrolysis. It was found to be immaterial whether the protein was hydrolyzed by ferments or with acids, provided that those atomic groups which were destroyed by the boiling with acids were replaced. The experiments were carried out on men, dogs, rats and mice, and not only was the nitrogen-balance maintained, but nitrogen was actually stored in the body. These results can hardly be interpreted otherwise than through the assumption of a synthesis of protein from the *Bausteine* which had been fed.

From these results follows the consideration of the second question as to how far the proteins undergo cleavage in the course of normal digestion. At present we are unable to answer this question with certainty. From the results of Borchardt we must assume that under certain circumstances even large protein complexes which still give the biuret reaction are capable of passage through the intestinal wall. Borchardt fed a cat with elastin, or hemi-elastin—its first decomposition product—and some hours after feeding was able to detect this latter albumose-like substance in the blood and organs of the animal. The detection of the hemi-elastin was rendered possible owing to the excellent precipitation reactions of this substance. Since we must regard elastin as a normal food constituent, the possibility of the absorption of these substances of high molecular weight must be admitted. But the possibility of the utilization of these substances for purposes of protein synthesis is by no means disproved. It is probable that the breaking down of these atomic groups may take place not only in the lumen of the gut or in the intestinal wall, but also in other organs. It is certain, however, that the conditions for a very far reaching decomposition of protein are most favorable in the intestine.

In the light of these results and with special regard to the ease with which proteins undergo both decomposition and synthesis in the animal and vegetable organisms we are led to consider the question of the importance of the proteins in metabolism rather from the point of view of their *Bausteine* than from the proteins themselves. Within what limits is it possible for one cleavage product to replace another? And are these cleavage products of unequal value from a metabolic point of view?

If these cleavage products were mutually interchangeable without restriction we should be obliged to infer that the proteins themselves were mutually interchangeable in metabolism. As a matter of fact we have long known that this is not the case. It is well known that gelatine cannot completely replace other food proteins, and it was natural to correlate this observation with the absence in the composition of gelatine of the two *Bausteine*, tyrosine and tryptophane. If this assumption were correct we should expect other proteins lacking in certain *Bausteine* to be incapable of serving as an exclusive source of protein food. My investigations with Kutscher have shown that the alcohol soluble proteins of cereals, for example zein, are free from lysine, and Hopkins and Wilcocks showed the absence of tryptophane as well. As a matter of fact Hopkins and Wilcocks and Henriques concluded from their experiments that zein was unable to replace completely other proteins in the food supply of mice and rats. Abderhalden and Glamser obtained similar results when they attempted to feed a dog with a mixture of substances derived by the complete hydrolysis of silk fibroin. The nitrogen balance was negative—that is to say, the cleavage products of silk fibroin were unable to serve as an exclusive source of protein nutriment.

Experiments of this character raise the question as to whether it is not possible to supply the missing cleavage products. As long ago as the seventies experiments were made in which tyrosine, tryptophane, cystine and other amino-acids were added to gelatin in order to determine their effect upon the nitrogen balance. The latest and most complete experiments of this kind were carried out by Abderhalden and Manolin. They found that in the case of the dog at least two-thirds of the protein nitrogen necessary for the maintenance of nitrogen balance could be obtained from completely hydrolyzed gelatin to which a certain quantity of other amino-acids had been added. Hopkins and Wilcocks had previously made experiments upon the feeding of mice with zein and their results indicated the importance of tryptophane in animal metabolism. Zein, as I have already mentioned, yields neither tryptophane nor lysine. They found that those mice which were fed upon zein as their sole protein food developed a peculiar condition of torpor which was not observed in the control animals. "For several days before death the mice were exceedingly inactive and made no movement when touched or handled. When in this condition the ears, feet and tail were cold to the touch, the eyes half closed and the coat glairy." The mice in all cases succumbed when fed upon zein without addition of tryptophane. On addition of tryptophane, however, they lived for a longer period. "The addition of tyrosine which is already present in zein has no such effect." That these phenomena were really due to lack of tryptophane was shown by the subsequent experiments of Henriques. He demonstrated the inability of zein to serve as a sole source of food protein. But, if, instead of zein, he fed another vegetable protein closely resembling zein in composition and, like the latter, yielding no lysine, he found that not only did the rats live but, when they consumed a sufficient quantity of the gliadin, nitrogen was actually stored. The most important difference in the composition of the two proteins is that gliadin contains the tryptophane group while zein does not. The importance of tryptophane is emphasized by the latest

experiments of Abderhalden. He fed dogs a mixture of the cleavage products of casein and brought the animals into nitrogen equilibrium. On feeding an equal quantity of cleavage products of casein from which the tryptophane had been removed, the nitrogen balance became negative, but on replacing the tryptophane nitrogen equilibrium was once more attained.

Hopkins and Wilcocks have suggested some very interesting views upon the rôle of tryptophane in animal metabolism. They consider that the fragments of the protein molecule may subserve other uses in the organism than "in the repair of tissues and in supplying energy. . . . . It is highly probable that the organism uses them in part for more immediate needs. . . . . Even when tissue equilibrium is not maintained, the presence or absence of some one amino-acid in the diet may affect most materially the survival period and general well-being of an animal." Accordingly the authors advanced the hypothesis that tryptophane "serves as a basis for the elaboration of a substance absolutely necessary for life—something, for instance, of an importance equal to that of adrenalin." They suggest that "the tryptophane is directly utilized as the normal precursor of some specific hormone or other substance essential to the processes of life." If the food materials do not contain the precursors of such hormones, the organism suffers injury, just as is the case when the organs forming the hormones cease to functionate.

While these experiments have shown that tryptophane is essential to the maintenance of life, Henriques' experiments with gliadin indicate that lysine may be dispensed with. One is inclined to assume that those protein *Bausteine* which possess a similar chemical constitution play a similar rôle in metabolic processes. The amino-acids of the aliphatic series may possess similar physiological significance. If we assume this, the fact that lysine may be replaced by homologous cleavage products becomes intelligible, whilst tryptophane stands in a class by itself both chemically and physiologically.

One may now consider the question of the possible conversion of one protein cleavage product into another, and also the possibility of the synthesis of these cleavage products themselves in the animal body. As a matter of fact investigations carried out during the last ten years have clearly demonstrated that the synthetic functions of the animal organism are not restricted to the assembling of ready formed protein fragments. As in the case of the vegetable organism, the formation of long carbon chains or of complicated heterocyclic systems from simple carbon compounds may take place in the body of higher animals. The prosthetic groups of the proteides are formed in this way. As an example of this I will refer to some experiments carried out in my laboratory a long time ago. Alexander Tichomiroff investigated the eggs of the silk-worm before and after the development of the young worms and found that purine derivatives, which are scarcely detectable in the undeveloped eggs, are present in large amounts in the bodies of the young animals. I obtained similar results in the case of hens' eggs.

A still more complicated prosthetic group is found in the red coloring matter of the blood. On decomposing this substance one can obtain dimethyl-ethyl-pyrrol and recent investigations have shown that four of these pyrrol rings united in a system containing thirty-four carbon atoms form the colored component of hæmoglobin. The formation of this complicated substance is effected not only in the body of the chick as soon as the area vasculosa is formed, but also takes place actively in the body of higher animals when, after severe loss of blood, it is necessary to replace the lost hæmoglobin. It is impossible to assume that the pyrrol derivatives necessary for this purpose exist preformed in the body.

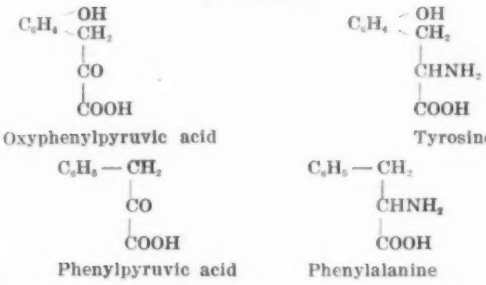
One may imagine that the synthetic activities of the body are regulated exactly according to the demands made upon it and that the power of ready synthesis is not made use of when the substance is contained in the food.

These questions gain in importance when we consider investigations which have been recently made upon the capacity of the animal body to form amino-acids. Experiments by Wiechowski and by Magnus Levy had already shown that the body could furnish more glycocoll than corresponded to the amount it had received. It would be possible to explain this in other ways than by synthesis, as, for example, by the breakdown of higher amino-acids. Knoop, however, has recently shown that nitrogen may be united with carbon with formation of an amino-acid in the course of animal metabolism. This reaction was observed on the administration of a ketonic or oxy-acid. Knoop made his experiments with γ-phenyl-α-ketobutyric acid and γ-phenyl-α-oxybutyric acid. From both of these substances the acetyl derivatives of phenyl-α-amidobutyric acid was formed and excreted in the urine. These experiments were extended by Embden and Schmitz. They perfused surviving livers with blood containing ketonic acids. In this way they demonstrated the formation of tyrosine from ρ-oxyphenylpyruvic acid, and phenyl-alanine from phenylpyruvic acid. Alanine was formed in good quantity from pyruvic acid and, as in the case of tyrosine and phenylalanine, was obtained in the naturally occurring optically active modification. Knoop concluded from his experiments that lactic acid which, as is well known, may be formed during muscular activity, and which has such a wide distribution in the body, might by a similar reaction be converted into alanine. Embden and Fellner were able to demonstrate this change by means of perfusion experiments. The following structural formulæ will render these reactions more intelligible.

TABLE VIII.

CH_3 | $CHOH$ | $COOH$	CH_3 | CO | $COOH$	CH_3 | $CHNH_2$ | $COOH$
Lactic acid	Pyruvic acid	Alanine
$C_6H_5CH_2$ | CH_2 | $CHOH$ | $COOH$	$C_6H_5CH_2$ | CH_2 | CO | $COOH$	$C_6H_5CH_2$ | CH_2 | $CHNH_2$ | $COOH$
Phenyl-α-oxybutyric acid	Phenyl-α-ketobutyric acid	Phenyl-α-amidobutyric acid

TABLE IX.



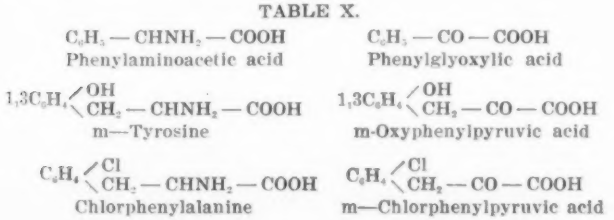
Embden was able to show that on perfusing a liver for an hour and a half a part of the glycogen was converted into alanine through the intermediate formation of lactic acid.

These results suggest that certain parts of the protein molecule originate from the carbohydrates. A similar relationship is indicated by the interesting observations of Knoop and Windaus upon the action of ammonia upon glucose, resulting in the formation of the iminazol ring—methylglyoxal being apparently an intermediate step in the reaction. The iminazol ring is characteristic not only for histidine but is also contained in the purine derivatives.

Investigations upon the fate of various constituents of the protein molecule undergoing decomposition in the animal organism have similarly revealed new and important relations existing between various tissue constituents. The detection of the intermediate steps in these rearrangements is of course only possible under special conditions. These conditions are found in cases in which the decomposition processes are incomplete because of disturbances of metabolism, like alcaptonuria and cystinuria. The same is true of experimental conditions permitting a separation of a part of the metabolic processes such as the perfusion of isolated organs, or of the study of chemical substances containing a nucleus or side-chain resistent to the disintegrating forces of the animal organism. This is the case with cyclic derivatives such as tyrosine, phenylalanine and tryptophane, either formed in the animal body or artificially introduced.

These substances first of all lose their amino group, which in the case of the protein derivatives are always found in the α-position. According to Neubauer and Flatow the amino group is replaced by oxygen so that a ketonic acid is formed from the amino-acid. This was observed in the case of phenylaminoacetic acid which was converted primarily into phenylglyoxylic acid when administered to rabbits. In the same way the feeding of m-tyrosine was followed by the excretion of a ketonic acid, m-oxyphenylpyruvic acid, while chlorphenylalanine gave chlorphenylpyruvic acid.

TABLE X.



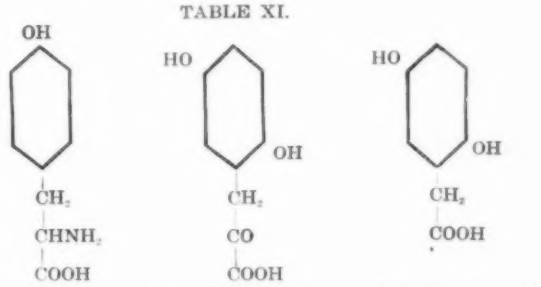
The process by which these substances are formed is the exact opposite of the previously mentioned synthesis of amino-acids in the animal body.

The further decomposition of the ketonic acids takes place with the removal of carbon dioxide and conversion of the CO into a COOH group.

Thus for example Neubauer showed that phenylpyruvic acid, derived from phenylalanine gives acetoacetic acid, when perfused through a surviving liver. The benzene ring is completely destroyed. The experiments of Dakin and Wakeman make it appear probable that of the four carbon atoms in acetoacetic acid two are derived from the benzene ring and two from the side-chain.

I may refer to the production of homogentisic acid. This acid is formed from tyrosine probably with intermediate production of hydroquinone-pyruvic acid, the three carbon side-chain being oxidized to an acetic acid group. At the same time another process takes place in the benzene ring—the hydroxyl group present in the p-position disappearing and two new OH groups appearing in positions 2 and 5.

TABLE XI.



A number of experiments have been made upon alcaptonurics in order to test these conceptions. Benzene derivatives of various kinds have been fed to persons showing this abnormality of metabolism in order to determine which of them are convertible into homogentisic acid. It was found that only those substances containing an amido or hydroxyl group or an oxygen atom attached to the centre carbon atom of the three carbon side-chain (*i. e.* in the α-position) were precursors of homogentisic acid.

Through the reactions previously mentioned an acid is formed containing one carbon atom less than its precursor which may then undergo further oxydation. In the case of normal carbon chains of the aliphatic series further oxydation takes place in the β-position. Carbon compounds with long chains of this kind occur in proteins to a limited extent only, as in lysine and in the ornithine contained in arginine. Knoop has drawn attention to the fact that arginine may yield guanidinebutyric acid which on oxidation would yield guanidineacetic acid. The latter substance, according to Jaffe, may be converted into creatin in the animal body by taking up the methyl group.

Investigations of this kind have demonstrated the formation of tissue products from fragments of the protein molecule.

This is also true of Friedmann's observations upon the formation of taurine from cystine.

When we consider the results obtained from the co-operation of chemistry and physiology, we notice certain marked changes in our ideas. Chemistry has shown that the proteins are made up of a certain number of units or *Bausteine* and that the differences in these *Bausteine* and the variations in their mode of linkage is responsible for the great variety of proteins. The resolution of a protein into simpler molecules or *Bausteine*, a process which is readily accomplished in the animal organism by means of ferments, involves the evolution of but little heat. Physiology has shown that the animal organism has not only the means of resolving the larger molecules into smaller ones, but also can bring about the reverse process. Furthermore it appears that the protein *Bausteine* play a rôle in animal metabolism not only as parts of the protein molecule but also as independent units. Feeding experiments have shown that glycocoll, ornithine and cystine may combine with certain substances administered to animals. In normal as well as diseased animals and especially in sprouting plants free amino acids of all kinds are to be found as well as more complicated molecules such as arginine, alanylhistidine and asparagine. There is no reason why the appearance of these substances should be considered solely from the standpoint of protein synthesis or decomposition. Hitherto the appearance of protein *Bausteine* in the living organism has always been ascribed to protein decomposition. But this supposition is unjustified. We must rather assume that these *Bausteine* may appear and disappear in the body without at any time forming part of a protein molecule. And further we may suppose that only under certain circumstances, for definite physiological purposes, are these independent groups stored in a collected form—the protein substances. This point of view does not exclude the possibility of the proteins as a whole taking part in important biological processes; but in general the problems concerning the proteins may be resolved into a series of simpler questions more accessible to research.

Thus the protein *Bausteine* are also the *Bausteine* of living material—of protoplasm. They are analogous to the other constituents of protoplasm which, like them, are capable when necessary of combining to form larger units—for example the phosphatides, the nucleins, fats and polysaccharides. All of these larger units are readily decomposed and as easily reformed by the tools of living substances—the ferments.

When we wish to consider the physiological rôle of protein substances, we must carefully distinguish between those cases in which the proteins act simply as the sum of their constituent *Bausteine* and those in which the special nature and mode of combination of these *Bausteine* are of greater importance. The use of protein as food is an example of the first case. The structural peculiarities responsible for the individuality of a given protein are destroyed by digestion and none of its characteristics remain except so far as they appear in the quantitative relation of its *Bausteine*. These *Bausteine* are absorbed and for the nutrition of the organism it is obviously a matter of indifference whether they arose from this or that combination. They are in all cases utilized according to the requirements of the organism.

If a protein reaches the body fluids without undergoing this process of dissolution, the conditions are altogether different. The protein may then exert special action depending on its structure. I would like to illustrate this by an example.

When arginine, valine or another *Baustein* found in the protamines is injected in rather large doses into the circulation the blood pressure is not particularly affected nor is any poisonous action observed. But W. H. Thompson has shown that if we inject into a dog 0.1 gram of a protamine formed by the union of these *Bausteine* there is a very considerable fall of blood pressure and paralysis of the respiration ending in the death of the animal. If we convert the protamine into protone by partial hydrolysis, the change involving a resolution of some but not all of the molecular combinations, it is found that the substance is physiologically almost inactive. The original protamine possessed the property of forming insoluble precipitates with other proteines in feebly alkaline solutions. The loss of this chemical property on dissolution of the protamine molecule is coincident with the loss of physiological activity.

This example shows us that by the union of various *Bausteine* groups may be formed conferring special chemical properties upon the whole molecule which can be recognized by their physiological actions. In the particular example cited the action was poisonous and harmful, but in other cases the effect produced by intact protein molecules may be a beneficial one. In all of these cases the action of the protein is not that represented by the sum of its *Bausteine*, but its properties are determined by its own structure. At present we cannot fully comprehend the rôle of the proteins, but we must assume that many of the enigmatical properties of living matter depend on this activity of *intact* protein molecules. We can obtain some idea of the possible variety in the combinations of the protein *Bausteine* by recalling the fact that they are as numerous as the letters in the alphabet which are capable of expressing an infinite number of thoughts. Every peculiarity of species and every occurrence affecting the individual may be indicated by special combinations of protein *Bausteine*, that is to say by specific proteins. Consequently we may readily understand how peculiarity of species may find expression in the chemical nature of the proteins constituting living matter, and how they may be transmitted through the material contained in the generative cells. Moreover it may be possible to obtain an explanation of the specific reactions of blood plasma based on the peculiarities of definite proteins; and by so doing we shall bring another group of phenomena nearer to chemical comprehension.

But it is not my intention on this occasion to follow the attractions of hypothesis at greater length. It must suffice to express the conviction that within the scope of protein chemistry we shall find new paths leading through the entire domain of biological research.

In conclusion, I wish to fulfill a pleasant duty in again expressing my thanks to my friend, Dr. H. D. Dakin, who has translated these lectures.

THE PATHOLOGY OF FAT METABOLISM.

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The accumulation of fatty substances in diseased cells is one of the most frequent of morbid changes. It is likewise one of the most generally misunderstood. It is a very widely held conception of the pathological processes which lead to the gross appearance of fat in cells that such fat is the direct product of protoplasmic degeneration. This conception, false though we now believe it to be, was taught by the text-books for more than fifty years, with the result that the term "fatty degeneration" has become, in the hands of the general medical writer, a careless designation for a variety of cell injuries associated with the appearance of fat. There are many terms in medicine which, like life preservers, are useful in an emergency. They have no precise, well-defined meaning and are often employed to enable a writer to make with ease a difficult landing. "Fatty degeneration" is such a term.

Fatty changes are in reality the most delicate indication of cell injury, with consequent impaired metabolism that we possess, but their correct interpretation demands a knowledge of the normal and abnormal metabolism of the fats.

The investigations of recent years have added richly to our knowledge of the pathology of fat metabolism, a result largely due to the application to the subject of chemical and physico-chemical methods. It is to some of the newer conceptions to which these advances have led that we shall devote our attention in this paper.

THE CHEMICAL NATURE OF THE FATTY SUBSTANCES FOUND IN THE BODY.

Until within recent years writers, in discussing the pathology of fat metabolism, have dealt with substances of simple chemical constitution, namely, the fatty acids, neutral fats and soaps. But we have gradually learned the great importance to the economy of another large and heterogeneous class of substances, the so-called "lipoids" or fat-like bodies, whose chemistry is by no means so simple or well understood. Exact chemical knowledge of the structures and properties of many of the substances classed as "lipoids" is still lacking; enough, however, is known to permit the bio-chemist to form a provisional classification. I shall follow, in so far as it seems of aid to the pathologist, the classification of fatty substances proposed recently by Rosenbloom and Gies.[1]

Ivar Bang[2] has defined "lipoids" as those compounds which are soluble in organic solvents, as ether, alcohol, chloroform, benzine, etc. It will be observed that this definition of lipoids embraces also the fats as usually understood. This immediately leads to confusion. Rosenbloom and Geis suggest the term "lipins" (analogous to proteins) as a substitute for "lipoids," and attempt a chemical classification of all fatty substances, similar to the present official classification of the proteins. Some of the terms which they use are new, but they are descriptive and do not differ confusingly from other designations now in use. The general adoption of these terms is not to be expected, may indeed be undesirable, but they furnish a logical working classification and as such have been employed in this paper. Their classification follows:

LIPINS (LIPOIDS).

I. Natural Aliphatic Lipins.

A. *Simple Lipins.*—All of these contain *carbon, hydrogen* and *oxygen,* but are free from *phosphorus, sulphur,* and *nitrogen.*

(a) Fatty acids, such as butyric and palmitic; various unsaturated acids as oleic and linoleic; and hydroxy acids of all these types.

(b) Salts and esters of the acids just spoken of in the preceding group.

(1) Soaps, as sodium oleate.

(2) Waxes.

(3) Fats and fatty oils. These neutral fats, or triglycerides, are esters of the trihydroxy alcohol, glycerol. Representatives of the class commonly found in the body are tributyrin, tri-palmitin and tri-olein.

B. *Conjugate Lipins.*—Natural compounds of simple lipins with non-lipin substances or radicles. All of these compounds contain *carbon, hydrogen* and *oxygen,* and practically all of them contain *nitrogen.* These substances, with those in Group II, A, constitute the group of so-called "lipoids"—a term without a definite chemical basis. (*Protargon* is a *mixture* of several conjugate lipins.)

(a) *Proteolipins.*—Compound lipins *containing protein radicles* (lecitho-proteins), such as lecithalbumins and ovovitellins. (These products may be only mechanical mixtures of proteins and lipins.)

(b) *Glycolipins.*—Compound lipins that are free from protein radicles but which *contain carbohydrate radicles,* such as the "cerebro-galactosids" represented by phrenosin. The substances in this group are *free from phosphorus* (Thudichum's "Cerebrosids").

(c) *Phospholipins.*—Compound lipins that are free from protein and carbohydrate radicles, but which *contain phosphoric acid radicles.* Lecithin, cuorin and sphingomyelin are examples (Thudichum's "Phosphatids").

II. Natural Carbocyclic Lipins.

A. *Sterols.*—Natural terpeno-alcoholic derivatives. They contain *carbon, hydrogen* and *oxygen,* but are *free from phosphorus, sulphur, and nitrogen.* Leading members of the group are *cholesterol,* iso-cholesterol, koprosterol and sitosterol. These substances are Abderhaldens "sterins," and with the conjugate lipins (Group I, B) constitute the so-called "lipoids."

B. *Esterols.*—Esters of sterols, such as cholesteryl palmitate in lanolin and cholesteryl oleate in blood.

C. *Cholates.*—Terpeno---acid derivatives of *hepatic* origin, probably from sterols or sterol radicles.

(a) Cholic acids (and their simple biological salts), such as cholic and choleic acids.

(b) Bile acids (and their biological salts), such as glycocholic and taurocholic acids.

The only other lipins of direct interest to the pathologist are the enigmatical "lipochromes," of undetermined composition, called by Rosenbloom and Gies chromolipins.

It is not possible in a paper of this kind to discuss in detail the separate classes of lipins; it will facilitate subsequent discussions, however, if we pause at this point to compare the structural formula of a typical simple lipin with that of a well-known conjugate lipin. Let us select one of the neutral fats, triolein, found so widely distributed throughout the body, and compare its structure with that of the conjugate phospholipin, lecithin, which likewise has a wide cellular distribution.

Triolein:

$$\begin{aligned} &CH_2O.OC.C_{17}H_{33}\\ &CH.O.OC.C_{17}H_{33}\\ &CH_2O.OC.C_{17}H_{33} \end{aligned}$$

Lecithin:

$$\begin{aligned} &CH_2O.OC.C_{17}H_{33}\\ &CH.O.OC.C_{15}H_{31}\\ &CH_2O.—P=O\\ &\qquad\quad OH \diagdown O.C_2H_4\\ &\qquad\qquad\qquad\quad > N(CH_3)_3\\ &\qquad\qquad\qquad\quad HO \end{aligned}$$

It will be noted, on comparing the two, that whereas in triolein the three hydroxyl groups of the tri-acid alcohol glycerol are replaced by three oleic acid radicles, in lecithin each of these hydroxyls is replaced by a different radicle. One of these radicles is probably always that of oleic acid, another that of some other fatty acid, while the third, which characterizes the substance, is a phosphoric acid radicle, which in turn is joined to the base cholin. In spite, however, of the more complicated structure of lecithin, it is obvious that it is very closely related to the simple neutral fats. Such a relationship reveals to us how the body may synthesize from relatively simple substances highly complex cell constituents. We are prone to think of metabolic processes as largely katabolic, whereas it is certain that anabolic synthetic processes precede the katabolic ones, often producing as end results very complex structures.

Cholesterol ($C_{27}H_{44}O.H_2O$) is another lipin which is a constant and important cell constituent. It is a mono-hydroxy terpeno-alcohol, and forms esters with fatty acids just as does the tri-hydroxy alcohol glycerol. Some of these esters exhibit very singular physical properties which we shall soon have occasion to study in more detail.

This brief chemical survey of the fatty substances will meet our present needs; those more interested in this phase of the subject will do well to consult the monographs of Bang and Leathes.[3]

We are fortunate in possessing several very reliable methods for the *morphological* study of fatty changes in cells. Just how fortunate we are will be the more appreciated when we contrast the relatively advanced condition of our knowledge of pathological fat metabolism with the almost utter ignorance which enshrouds the subject of cloudy swelling of cells. In another place[4] I have discussed the relative merits of the various methods for the morphological study of fatty substances, and since the necessary details are readily accessible in the technical manuals, these methods, important though they are, need not detain us at this time.

The Physiological Occurrence of Lipins in the Body.

There is a question, often neglected, but of the greatest importance, in a study of pathological fatty changes in cells, which is directly connected with the morphological study of of fatty cell-inclusions, and that is the physiological occurrence of fat in the various cells of the body. The lipins are one of the three great sources of the body's food supply, and they are normally present in some form in all cells. It is not generally recognized, however, that microscopic fat globules may be present physiologically in varying amounts in all gland cells. Cells of this type are not using their maximum energy all the time, hence it is quite common for a gland like the pancreas, for example, to show very considerable variations from time to time in its microscopically visible fat-content.

This phase of the question is well illustrated by the conditions present in seminiferous tubules of the normal testicle. Such a testicle, stained for fat, shows in certain tubules not actively engaged at the time in sperm-formation, many rather large fat globules situated in the Sertoli cells. These globules are usually ascribed to a "fatty degeneration" of the Sertoli cells. With the advent of spermatogenesis, these large globules break into smaller ones and gradually pass into the spermatocytes and spermatids. As this takes place, the fat alters its character from that of a neutral fat, or simple lipin, to one of the more complicated conjugate lipins, probably lecithin. The fully matured spermatozoa are peculiarly rich in fatty matter which further strengthens our belief that the fat assimilated by the Sertoli cells, or sperm-nourishing cells as they are called, is used during spermatogenesis as nutriment for the developing spermatozoa. The conditions found in cryptorchid testes furnish additional proof of what has just been said. In this condition, as is well known, all cells of the sperm-forming series have completely disappeared, thus removing the normal physiological outlet for the fat assimilated by the Sertoli cells. As a consequence, the Sertoli cells become engorged with neutral fat droplets, and chemical anaylsis shows that the percentage of fats in cryptorchid pig testes is almost double that found in the normal organ. Here again authors insist that the Sertoli cells are in a condition of "fatty degeneration," and this despite the fact that such Sertoli cells contain healthy nuclei, and nowhere present evidences of cellular disintegration.

Examples of such errors arising from a failure to appreciate the rôle of fatty substances in the body's metabolism could be

multiplied. It is not so long ago that the adrenal was regarded as showing a constant normal "fatty degeneration" of its cortex, and the corpus luteum cells were thought to be in the same desperate condition.

The fat which is assimilated by the healthy cell is quickly changed to a combined state in which it is no longer possible to render it visible by any micro-chemical means at our disposal. This combined fat forms a large item among the total constituents of the cell. The kidney normally contains from 15 to 23% (dried weight) of fat in this invisible condition. Now the fat deposited in the great fat-depots of the body (subcutaneous and subserous tissues, omentum, mesentery, peri-renal fat, etc.) is readily available for the body's nutriment, and disappears with starvation. It is *labile* fat. Fat in the invisible, combined condition of which we have spoken is on the contrary highly *stabile*, the cells clinging to it with the greatest tenacity even in extreme starvation.

The Pathological Occurrence of the Simple Lipins.

We have seen that the term "fats" in its broader modern meaning includes a great variety of substances which vary considerably from each other in their chemical constitution. Their solubilities in organic solvents, however, separate them fairly sharply from the carbohydrates and proteins, and permit of their classification in one large heterogeneous group. These fats, or lipins, are primary and essential constituents of the cell, and occur, with quantitative and qualitative variations, in all the cells of the body. They may or may not be microscopically visible.

It remains for us to consider the occurrence of the various kinds of lipins throughout the body under pathological conditions. This is at once one of the most interesting and difficult of pathological problems, and, in spite of recent great advances, it is by no means a closed chapter.

In the first number of his Archiv (1847) Virchow divided the forms of pathological fatty changes into two groups—fatty infiltration and fatty degeneration. Virchow taught, as the term fatty infiltration indicates, that fat may infiltrate a cell from without, the cell remaining healthy, and perfectly capable of returning under more favorable conditions to its normal state. This change he considered to be only a slight deviation from the physiological fat-infiltration seen in adipose tissue, or from the fatty infiltration of the intestinal mucosa and liver during digestion.

Fatty degeneration, however, he conceived to be a far more serious lesion of the cell—a true necrobiotic process. "Unter den nekrobiotischen Prozessen ist der unzweifelhaft am weitesten verbreitete und fast wichtigste im Verlaufe aller bekannten cellularen Störungen die fettige Degeneration." ("Die Cellularpathologie, etc.," 1862.)

He regarded the accumulation of fat in this condition as due to a direct degeneration of the cell protoplasm into fat. This conception has become classical, and has been, until very recently, the orthodox teaching. Whether this doctrine is absolutely erroneous or not is impossible to state with certainty. It is assuredly quite conceivable that fat may be derived from so huge a complex as the proteid molecule, and indeed some bacteria and fungi are capable of effecting this change, but there is not the slightest evidence that such a transformation ever takes place in the body. There is, on the contrary, a great deal of excellent evidence that the accumulation of fat in cells is always an infiltrative process. Some of this evidence we shall now review.

Cell injuries caused by a great variety of substances are associated with fatty accumulations. Conditions such as phosphorous and arsenic poisonings; intoxications with bacterial toxins, especially when accompanied by fever; the excessive use of alcohol; deranged function of certain glands with internal secretions; the various types of anemia—these and many other conditions may cause cellular injuries which are accompanied by visible fatty accumulations.

Confronted with the fatty liver of phosphorous poisoning, or of chronic alcoholism, or with the fatty mottled heart of pernicious anemia, what proof have we that the abnormal amounts of fat which are so obvious represent infiltrations from extra-cellular sources, and are not derived from the transformation of the cytoplasm of the injured cells into fat? This question has provoked a tremendous amount of investigation, some results of which are among the most brilliant of medical science.

Lebedeff, in 1883, was the first to oppose Virchow's conception of "fatty degeneration" with substantial scientific proofs. He fed starved dogs on linseed oil and, after phosphorous poisoning, found the fatty condition of the liver largely due to the presence of this oil. Lebedeff concluded that the fatty liver of phosphorous poisoning was due to a mobilization of the depot-fats in the liver, and other organs. It is a surprising fact, but nevertheless true, that an animal fed upon a foreign fat will store this fat largely as such in its fat-depots. This result has been repeatedly confirmed.

Some fourteen years later Rosenfeld, in a series of very careful researches, demonstrated conclusively this transportation of fat in phosphorous poisoning, and since then many confirmatory details have been added by other investigators. One of Rosenfeld's striking experiments was this. He starved dogs until their body fat could not be further reduced, and then fed them lean meat and an easily identified foreign fat, such as linseed oil (which has a low melting point and can combine with much iodine) or mutton tallow (which has a high melting point and a low iodine number). Under these conditions, the animals stored the foreign fat in their fat-depots and liver. After a few days' starvation (to remove the fat from the liver) the animals were poisoned with phosphorus, which produced a fatty condition of the liver and other viscera. An examination of this fat revealed that it was not typical dog fat, as it should have been if it were a result of proteid degeneration, but was largely composed of the foreign fat which had been previously fed. Furthermore, animals which were in a state of starvation failed to develop fatty livers when poisoned. These and other interesting results have been confirmed by Febiger in chickens and rabbits, and by Taylor, and Athanasiu, in frogs.

It seems well established, then, that in fatty cellular changes we are dealing with a process of fatty accumulation or infiltration and not a degeneration in the sense of Virchow. There is likewise much morphological evidence for this view, but we need not pause to discuss it at this time.

Upon analyzing organs showing typical fatty infiltration and comparing their total fat with the fat content of normal organs, Rosenfeld made the seemingly contradictory discovery that the total fats of a fatty infiltrated organ are not greater in quantity, and may be less, than normal. All the facts, however, are easily harmonized by a consideration of the metabolism of the normal cell.

Fat is being constantly taken up from the nutritive fluids of the body either as soluble fat, or as glycerol and fatty acids, which latter may be in the form of soaps. This fat is contained in the cell in an invisible form, probably in chemical combination, for as has been noted, a kidney which contains no visible fat under the microscope may yet contain normally from 15 to 23% (dried weight) of fat upon extraction. This is the stabile fat of which we have spoken, and it is in part so firmly bound to the proteins that peptic digestion is necessary for its complete liberation. Now the assimilation of fat, and its further utilization by the cell, are certainly two largely independent processes. Normally, they are nicely regulated so that the intake and utilization balance. But if the cell is poisoned or if through anemia its oxidative powers are decreased, this metabolic balance is disturbed. Fat continues to enter the cell through the activities of the highly resistant cell lipase, but once there, the disorganized dissimilative functions of the cell are unable to utilize it—fat accumulates. We may not in the given instance of a certain toxin be able to say just what injury it produces in the cell which disturbs the normal fat metabolism; our ignorance of the normal structure and metabolism of the cell is too profound for that. But it requires no great flight of imagination to conceive that substances so foreign to the normal content of a cell as arsenic or chloroform or bacterial toxins, may produce very great alterations in the physical and chemical constitution of the cell, with consequent disturbance of metabolism. An explanation of Rosenfeld's observation that fatty-infiltrated organs may show no increase in their total fats follows from what has been said. It is an accepted biologic principle that cell intoxicants act primarily as stimulants to increased metabolic activity. Hence we may accept that the first effect of a poison will be an increased demand for food on the part of the cell. In response to this demand, fat leaves the storehouses and is carried by the blood to the various organs. The injured cells are using more fat, and until the injury actually advances to a degree where metabolism is seriously disturbed, the increased intake of fat is speedily utilized. If the intoxication is severe, however, a time soon comes when some cells are no longer able to convert the fat taken from the blood into the invisible, combined form. It is conceivable, however, that fat which has already been elaborated by the cell is subsequently utilized, so that while we see more and more fat, it does not necessarily follow that in the end the affected organ will contain absolutely more fatty matter. If the injury ultimately results in a complete destruction of the normal molecular arrangement of the cell, some of the combined fats present in the nucleus and cytoplasm will become visible. That is apparently what happens in post mortem autolysis, a subject to which we shall soon return. The accumulation of fat in the cells of the body is, however, a vital process; dead cells may show fatty deposits, but it seems certain that such fat was assimilated during the life of the cell and not after death.

The Pathological Occurrence of More Complex Lipins.

In the foregoing discussion of fatty infiltration the term fats (or lipins) has been employed without seeking to be more specific, following the usage which prevailed until within recent years. Now, however, it is necessary to consider the pathological occurrence of not only the neutral fats, fatty acids and soaps, but of some other very important members of the group of lipins. Only a few of these are chemically well defined enough to permit at present of very exact studies. They present to both the chemist and the pathologist serious difficulties in that they are usually present as mixtures, the components of which mutually influence each other, and many are soluble in exactly the same solvents, rendering their separation difficult and often impossible.

The nomenclature of new and complex subjects is often involved, and the terminology of the lipins is no exception to the rule. Some writers speak of "fats and lipoids" in an attempt to separate the neutral fats, and their components, from the remaining lipins. Others use the term lipoid as a collective name for all fatty substances. Both usages are inexact and misleading. It seems to me that we can only hope to escape unnecessary confusion by adopting some classification embracing all fatty substances, and then refer by name to the separate members of the group. This I have tried to do by adopting what seems to be the most helpful classification available. In a subject which is so rapidly advancing, any classification must be recognized as largely tentative and provisional.

Aside from the simple lipins (neutral fats, fatty acids and soaps), only two other groups need enter into a pathological discussion of the lipins. These are the phospholipins (phosphotids), which are characterized by the presence of a phosphoric acid radicle in their molecule (one of the lecithins will serve as an example), and the compounds of the terpeno-alcohol, cholesterol.

All fatty changes in living cells are the result of infiltration, that is, the fats are of exogenous origin. The character of these fatty substances varies, however, and it is very important for us to learn to detect the different varieties of lipins which are encountered under pathological conditions in the body, for they are of varied significance. There is one characteristic of certain lipins which permits their detection at once, even when they are mixed with others. For example, if we scrape some of the fatty, necrotic material from an area of arteriosclerotic degeneration and examine it under the microscope, we shall find among the detritus masses of fatty matter and

cholesterol crystals. Upon examining the same specimen between the crossed Nicol prisms of a polarizing microscope a singularly beautiful phenomenon is observed. Standing forth from the intense blackness of the unilluminated microscopic field are many small, brilliantly glistening, globular bodies, many of which on closer examination, show a dark Maltese cross dividing the globules into four highly refractile sectors. This is the phenomenon of double refractivity or anisotropism and is a property of crystalline substances. The globules which we have just described, though, are fluid, for they constantly assume, especially on warming, a spheroidal shape and are mobile. They are indeed *fluid crystals*, as was first pointed out by Adami and Aschoff. Physical chemists are familiar with many such bodies (Lehmann: Flüssige Kristalle. Leipzig, 1904). Their solubilities in fat solvents and their staining reactions leave no doubt that these anisotropic globules belong to the group of lipins.

Kaiserling and Orgler first directed modern attention to these peculiar anisotropic lipins, and they have been carefully studied by Aschoff,[5] Adami,[6] Kawamura[7] and others. It seems fairly well established that whereas several individual lipins, and mixtures of these, may show anisotropism (as for example certain soaps, sphyngomyelin and possibly lecithin, phrenosin,* cholesterol and cholesteryl esters), only certain of these substances, namely, cholesterol and its compounds, show constantly and typically the phenomenon of double refractivity at the temperature of the body. This has led Aschoff to divide fatty infiltration qualitatively into "Glycerinesterverfettung" and "Cholesterinesterverfettung." Certain other characteristics aid in the differentiation of cholesteryl esters. When they are warmed the phenomenon of anisotropism disappears, only to return on cooling in a more outspoken and beautiful fashion. Other lipins showing anisotropism do not lose this property on warming. Cholesterol compounds are less soluble than neutral fats in the ordinary fat solvents, and stain rather yellow than red with Sudan iii. They become gray rather than black when treated with osmium tetroxide. On freezing, or fixing in formalin, they may assume solid crystalline forms, which on warming pass again into the globular, fluid crystal phase. Most other fixatives destroy at once this anisotropic property, and it is not seen after staining with the usual fat-stains. It remains after staining with Nile blue sulphate. Material to be examined for anisotropic lipins may be teased in the fresh state and examined in glycerin or water, or where the maintenance of histological relations is desired, frozen sections may be employed.

Anisotropic substances are physiologically present in visible form in only four organs, namely, the adrenal cortex, thymus, ovary (corpus luteum) and testis (interstitial cells). Their function has not been determined, but it seems, in the case of the adrenal at least, to be one of importance to the organism.

Pathologically it has been found that anisotropic fatty substances occur only in more or less chronic conditions, and their occurrence is always associated with the actual necrosis of cells. They do not occur in acute diseases (Munk, Kawamura). They are found most frequently in the neighborhood of chronic inflammatory processes, as for example, in the mucosa of the Fallopian tubes in chronic gonorrheal infection, or the gall bladder mucous membrane in chronic cholecystitis. They are commonly found in chronic nephritis. One frequently sees a multitude of small yellow flecks on the surface and in the substance of a cirrhotic kidney, and examined under the polarizing microscope these are found to contain abundant anisotropic fat globules. Amyloid kidneys are especially rich in anisotropic lipins.

Caseous tuberculous areas do not contain anisotropic bodies, but in the neighborhood of such tuberculous foci many small yellow areas filled with doubly refractive substances are often seen. We recently found in the neighborhood of a gangrenous portion of a lung many small deep yellow areas which seemed to occupy alveolar spaces. On examination these were found to be largely composed of desquamated alveolar cells filled with anisotropic substances. The so-called myelin cells found in the sputum in chronic bronchitis, especially chronic influenzal bronchitis, and in catarrhal desquamative pneumonia are alveolar cells and leucocytes filled with anisotropic lipins. Anisotropic lipins are said not to be present in tuberculous salpingitis, whereas their occurrence is quite the rule in gonorrheal salpingitis.

For the sake of completeness, the following conditions may be mentioned in which anisotropic substances have been described: arterio-sclerosis, puerperal uteri, choroid plexus, pyosalpinx, pyometria, purulent membranes, in pyelitis, mesenteric cysts, actinomycosis, chronic mastitis, cholangitis, albuminuric retinitis, xanthoma, the urine and many tumors (carcinoma, sarcoma, hypernephroma, adenoma, etc.).

The anisotropic lipins frequently occur in seemingly intact cells, and are regarded by those most experienced as infiltrations. Cells which are obviously in a condition of necrobiosis often contain anisotropic substances, but we cannot conclude from this that such substances are the result of the decomposition of the containing cells. This would be an indefensible repetition of Virchow's error in regard to fatty degeneration. That anisotropic fats are the result of a vital infiltration and are not the result of protoplasmic degeneration has been shown by the careful chemical work of Windans. He found the amount of cholesterol and of cholesteryl esters far above the normal upon comparing arterio-sclerotic aortas, and kidneys showing chronic nephritis with the normal organs. This can only be interpreted as an infiltration of cholesterol either as such or as an ester, for there is no more proof that cholesterol is derivable from proteins than there is of such an origin for the neutral fats. The problem is the same in both cases. Anisotropic substances may be present in parenchyma cells, as for example those of the convoluted tubules of the kidney; they are found in the endothelial cells of lymph vessels, and occur free in the tissue spaces and lymphatics. Ordinary isotropic neutral fats are almost always mixed with the anisotropic, and usually the former predominate.

What is the source of these peculiar complex lipins, and why are they found only in subacute or chronic conditions associated with the necrobiosis of cells? It is well to admit

at once that answers to these questions are of necessity, at the present time, partially speculative. Much careful chemical and pathological investigation will be required to answer them with certainty. The lipins both simple and complex are, as we know, essential and constant constituents of the cell. They form the covering membranes of the nucleus and cell granules (Albrecht, Faure-Fremiet) and have been shown to be most important factors in the osmotic interchanges between the cell and its environment (Meyer, Overton).

Anisotropic lipins are formed very slowly and are in all probability the result of chemical and physical rearrangements of the lipins derived from broken-down cells whose disintegration has been very gradual. They accumulate in adjacent living cells probably as a result of the same factors which are operative in the production of ordinary (glyceryl ester) fatty infiltration. Phagocytosis by both the wandering and fixed cells must also be considered a factor in the assimilation of fatty substances. The cell, itself, then, is one source from which complex lipins may come, and this is probably the explanation of the frequent association of visible deposits of these substances in the neighborhood of necrobiotic processes.

It must also be borne in mind, as Aschoff points out, that the compounds of cholesteryl esters are contained in the blood plasma, and may under certain conditions accumulate in cells. Xanthoma cells are examples of this infiltration from the blood.

Finally there is a fatty change in cells which takes place during autolysis, and which is to be sharply differentiated from the other fatty changes that we have studied. Organs free from microscopically visible fat when allowed to undergo aseptic autolysis show after a time many small refractile granules of a fatty nature (Waldvogel, Dietrich). These have been termed myelin droplets and they are quite different from the fatty substances which appear in cells during life. They are not doubly refractile and yet differ in their solubility and staining reactions from the neutral fats. They stain with neutral red (Albrecht) and this has led to the belief that they are composed in part at least of fatty acids which have been set free from the lipin compounds present in the nucleus and cytoplasm. Here for the first time we meet with intracellular substances of a fatty nature which are clearly of immediate endogenous origin. The process has been termed "myelinic dissociation," and is to be regarded as a molecular decomposition of the cytoplasm, during which the combined fats of the cell become visible. To these fatty substances which appear post mortem in the cell, the purely physical designation "myelin" has been applied. Their exact chemical composition is unknown. One very interesting property of these so-called myelin droplets is that upon the addition of water, they swell into a great variety of bizarre forms. These "myelin figures," as they are called, are not peculiar to post mortem droplets; one can demonstrate them quite beautifully by adding a solution of ammonia to a drop of oleic acid, and observing the edge of contact under the microscope.

Myelin droplets are seen in cells which show the condition of cloudy swelling, and this suggests that in cloudy swelling we may be dealing with an ante mortem autolysis of the cytoplasm. Cloudy swelling could thus be regarded as one of the earliest indications of cellular necrobiosis, and there is much to be said for this view.

To recapitulate:

1. The large group of fatty substances which, following Rosenbloom and Gies, we have called lipins, embraces besides the neutral fats, fatty acids and soaps, a number of more complex substances which occupy a place of great practical importance in the study of the normal and abnormal metabolism of fats.

2. Lipins are constant cell constituents and occur in both visible and invisible forms. The invisible form usually predominates in the healthy cell, but various cell injuries are accompanied by visible accumulations of lipins.

3. Such fatty accumulations are not the result of a degenerative transformation of the cytoplasm into fat, but represent deposits of lipins which, owing to some injury, the cell cannot utilize. The term "fatty degeneration" should be discarded as erroneous and obsolete.

4. All visible accumulations of lipins occurring in living cells are to be regarded as infiltrations, and they may be physiological or pathological.

5. Pathological fatty infiltrations may be divided for purposes of study into

(a) Glyceryl-ester infiltrations.
(b) Cholesteryl-ester infiltrations.
(c) Infiltrations of other lipins.

Glyceryl-ester infiltration indicates an injury to the containing cell, while cholesteryl-ester and other lipin infiltrations are indicative of the necrobiosis of neighboring cells.

6. Cholesteryl-esters assume fluid crystalline, anisotropic forms in the body and the presence of such anisotropic accumulations are characteristic of chronic degenerative lesions.

7. During autolysis, the invisible lipins of the cell assume a visible form, but they differ characteristically from the lipins which are deposited in cells during life. The process is termed myelinic decomposition or dissociation and has no connection with the process of fatty infiltration.

BIBLIOGRAPHY.

1. Rosenbloom and Gies: Biochem. Bull., 1911, I, 51.
2. Bang, I.: Chemie und Biochemie der Lipoide. Bergmann, Wiesbaden, 1911.
3. Leathes: The Fats. Longmans, Green & Co., 1910.
4. Hanes and Rosenbloom: J. Exp. Med., 1911, xiii, 355.
5. Aschoff: Beitr. z. path. Anat., 1910, xlvii, i.
6. Adami: Harvey Lectures, Philadelphia, 1908, II, 117.
7. Kawamura, R.: Die Cholesterinesterverfettung. Fischer, Jena, 1911.

Detailed references to the literature have been purposely omitted from the text since they are readily available in exhaustive form in the monographs of Leathes, Bang, and Kawamura.

PROFESSOR SAMUEL D. GROSS: AMERICA'S FOREMOST SURGEON.[1]

By C. W. G. ROHRER, M. A., M. D., Ph. D., Baltimore, Md.

It was the late Bishop Phillips Brooks who said: "If I ever wrote a book I would want it to be a biography, portraying a great man's life." To-night I shall make a feeble attempt to outline a life-history of the manner of man indicated by Bishop Brooks.

BIRTH AND PARENTAGE.

Samuel David Gross, the subject of my sketch, was born near Easton, Northampton County, Pennsylvania, on the 8th of July, 1805. The original Gross homestead, about four miles from the city of Easton on the Northampton Pike, was a fine farm embracing two hundred acres of the best land, in a high state of cultivation. Upon it was a large orchard famed for the abundance and excellent quality of its fruit. Besides the other necessary farm buildings, this tract of land was improved by a two and one-half story stone house, a portion of which is still standing. It has long since passed into the hands of strangers, and is now known as "Chesterfield Farm." The old stone house has been remodeled and rebuilt, and is occupied by the gardener. Within its quaint walls Dr. Gross first saw the light of day; from its rude doorway he went forth an humble country lad, to eventually become America's foremost surgeon.

Philip Gross, his father, was a man of sterling worth. He was one of the most highly respected citizens in Eastern Pennsylvania. He was tall, handsome, and of dignified bearing. His son, the Doctor, inherited his father's physical beauty and manly traits. The father died of apoplexy in November, 1813, at the age of fifty-six, when his son was in his ninth year.

Juliana Gross, his mother, was, before her marriage, a Brown; she died of asthma in March, 1853, at the advanced age of eighty-six years. She is described as a woman of lovable character, and an excellent wife and mother. Her son attributes much of his professional success to the training which he received at his mother's knee, and to the influence of her exemplary life. Both parents were of German descent, and natives of Pennsylvania.

Dr. Gross had two sisters and three brothers. One of his brothers, the Rev. Joseph B. Gross, was for many years a well-known clergyman of the Lutheran Church, to which religious sect the Gross family for generations had belonged.

BOYHOOD AND YOUTH.

His boyhood and youth were pleasantly spent on the farm. Living much of the time out of doors, he early acquired a fondness for natural history. In the eloquent words of a gifted poetess, Gross at a tender age found

> Tongues in trees, books in running brooks,
> Sermons in stones, and good in everything.

The usual sports and amusements incident to country life were also enthusiastically engaged in by him. Target shooting with a "bow-gun," ball playing, pitching quoits, rabbit-snaring, snow-balling, pitching pennies, and hunting bird's nests were favorite forms of amusement, each in due season. He believed that the skill which he acquired in pitching quoits contributed much to his manual dexterity and surgical acumen. As a boy he was excessively fond of fishing. Another favorite amusement with all country boys is fighting bumblebees, wasps, hornets, and yellow-jackets. In this type of sport, though sometimes resulting in all the cardinal symptoms of inflammation, he soon became an acknowledged leader.

His favorite books were the Bible, Aesop's Fables, and Witches of the Hartz Mountains. Like his illustrious fellow-countryman, Benjamin Franklin, he also read various almanacs, volumes of history, geography, and romance.

Before the age of six years he made known to his parents that he wanted to be a physician. This early impulse permeated the very fibre of his being. It came to him like an inspiration, and dominated the entire period of his childhood and youth; nor did it cease its prompting until it had in a measure been fulfilled.

EARLY EDUCATION.

Dr. Gross obtained the first rudiments of his education at a log-cabin school house located nearly a mile from his home. Here the three R's—Reading, 'Riting, and 'Rithmetic—were taught, as well as the simplest rules of spelling. He soon became an apt pupil, and showed signs of good scholarship. Notwithstanding these hopeful indications, his early advantages were but meagre. As a result, his preliminary education was noticeably defective.

However, there still burned within his boyish heart the desire to be a physician. He had now attained to an age where he could see the defect in his common school education. He was industrious, he was ambitious, and he was imbued with a goodly amount of characteristic German thoroughness. At this juncture he set resolutely to work and took up the study of three languages—Latin, German, and English. He also made commendable progress in reading, composition, and arithmetic.

At the age of seventeen he considered himself fitted to begin the study of medicine. In those days it was customary to "read medicine" in the office of a physician, a practice now almost obsolete. Accordingly he entered the office of a country physician. Receiving but little aid, he withdrew from this practitioner's office and tried another. The result was the same, and he again sought a new preceptor. His third attempt proved subsequently to be equally disastrous. This time

[1] Paper read at the meeting of the Johns Hopkins Hospital Historical Club, January 15, 1912.

In the preparation of this paper I have received valuable assistance from the following persons: Dr. Gross's only surviving son—Mr. A. Haller Gross of Langhorne, Pennsylvania; Dr. W. W. Keen, Dr. J. W. Holland, and Mr. Nelson Alexander Chestnutt of Philadelphia; Dr. Edgar M. Green, Miss Swift, and Mr. Reuben Kolb of Easton, Pennsylvania; and last, but by no means least, my photographer, Mr. Harry B. Weaver of this city.

he had applied to Dr. Joseph K. Swift of Easton, a graduate of the University of Pennsylvania. Dr. Swift is characterized as "an eminent physician and surgeon and a highly cultivated gentleman."

For a brief season the current of the would-be medical student's life ran smooth. No angel "troubled the pool." But it was merely the calm which precedes the storm. To use Dr. Gross's own words:

> With the aid of Fyfe's Anatomy and a skeleton, I learned some osteology; but even this was up-hill business, and I at length gave up in despair. I found that my Latin was inadequate, and that I could not understand the technicalities of medicine without some knowledge of Greek. *This was the turning-point in my life.* I had made a great discovery—a knowledge of my ignorance; and with it came a solemn determination to remedy it.

He did not stand alone in his great discovery. His preceptor, Dr. Swift, was not slow in establishing priority by the reply which he made. According to information which I have received from his grandniece, Miss Swift,[2] when Gross, at that time a country boy, communicated his views to his preceptor, the result far exceeded his most sanguine expectations. Dr. Swift paid him anything but a flattering compliment by telling him "to get an education first, and then study medicine."

He met the situation bravely; relinquishing his medical studies for the time being, he entered college. Wilkes-Barre Academy was the school selected, and here he remained for one year. He next attended a classical school in the city of New York. Becoming dissatisfied, he returned at the end of six months to Easton, where, under the tutelage of his former teacher, Mr. Joel Jones,[3] he took up the study of Latin and Greek. By the end of another half year he longed to return to college to complete his classical studies, and so he went to the Lawrenceville High School, in the State of New Jersey, where he rounded out his preparatory education in a satisfactory manner.

Medical Training.

At the age of nineteen years he began in earnest the study of medicine. In his Autobiography, written shortly before his death, Dr. Gross comments upon the difficulty of choosing a profession. He says: "The choice of a profession is one of the greatest perplexities of a young man's life." Not so, however, in his case, for he was determined from his earliest boyhood to study medicine. From its very incipiency he was wide awake to the seriousness of the proposition. He either may have grasped the situation intuitively, and realized that his was the most laborious and most exacting of the three learned professions—divinity, law, and medicine—or, perhaps, he called to mind the saying of Cicero, that, "In no way do men approach nearer the gods than in trying to give health to their fellowmen."

He began again the study of medicine under Dr. Swift at the age of nineteen. He applied himself diligently for nearly a year, at the expiration of which time his health broke down. Accompanied by one of his brothers, he rode to Niagara on horseback to recuperate. At the end of six weeks he was as well as ever, and returned to his studies. In October, 1826, he proceeded to Philadelphia, and immediately enrolled himself as a private pupil of Dr. George McClellan,[4] professor of surgery in Jefferson Medical College, and several weeks later he matriculated at Jefferson Medical College.

Gross was an indefatigable and painstaking student; whatsoever his hand found to do, he did with his might. The medical student of to-day could not do better than copy his example. Concerning his ne'er-to-be-forgotten medical student days he thus writes in his Autobiography:

> I worked early and late, and lost no occasion to profit by the opportunities that were afforded me. I was determined to qualify myself well, especially in the practical branches. I was very fond of anatomy and surgery, and therefore made them objects of particular inquiry. During the eighteen months of my connection with McClellan I had witnessed many important operations, and had seen a good deal of medical practice. My mind, too, was well disciplined; I had not only industry, but ambition; my morals and habits were good, and I was a stranger to all amusements. Medicine was the goddess of my idolatry.

He was graduated from Jefferson Medical College, in the year 1828. He had attended three sessions of the college, and was one of a class of twenty-seven to receive the honors of the doctorate. His graduation thesis was on the Nature and Treatment of Cataract. The commencement address to the graduates was delivered by his preceptor, Dr. McClellan.

Professional Career.

After a short visit to his mother at Easton, Gross returned to Philadelphia, which city he determined to make his future home. He opened an office at the corner of Library and Fifth streets, immediately opposite Independence Square, and announced himself as a candidate for business. As is usually the case with a young physician, especially in a large city, practice came slowly, but he was not idle. He improved his leisure moments by translating four foreign works on medicine and surgery, to which I shall again refer.

After a vain struggle of eighteen months in the "City of Brotherly Love," he found himself in financial straits. His patrimony was exhausted, and the income from his practice scarcely exceeded three hundred dollars. There was but one alternative—to return to Easton, where living expenses were lower and a young physician's opportunities greater. Accordingly, in April, 1830, he returned to Easton to take up the burden of life again amid the scenes of his nativity. Here he gradually acquired practice, and in a year or so he was regarded as a scientific physician. His office was on Centre Square, opposite that of his old preceptor, Dr. Swift.

[2] It is interesting to note that his sign (or "shingle," as we sometimes call it), weather-beaten and old, still adorns the door-panel of Miss Swift's comfortable home in Easton.

[3] Subsequently elected to the judgeship.

[4] Dr. McClellan's life story is soon told: he was great as a medical teacher, great as a surgeon, the founder of Jefferson Medical College, Philadelphia, the preceptor of Dr. Gross, the father of the late General George B. McClellan, and grandfather of ex-mayor McClellan of Greater New York.

DR. GROSS IN HIS PRIME.

PORTRAIT OF DR. GROSS
IN LIBRARY OF JEFFERSON MEDICAL COLLEGE.

THE GROSS HOMESTEAD.

"Within its quaint walls Dr. Gross first saw the light of day; from its rude doorway he went forth an humble country lad, to eventually become America's foremost surgeon."

His interest in practical anatomy never abated one jot. In the rear of his Easton home there was a garden; at its foot he had a small stone building erected, which he used for a dissecting room. A human subject was occasionally procured from Philadelphia, which he himself transported to Easton in a buggy. Numerous unsuspecting cats and dogs also fell a prey to his thirst for anatomical investigation.

The following incident which occurred while he resided in Easton is authentic. It was communicated to me by Dr. Edgar M. Green, a son of the late Dr. Traill Green, and one of the most prominent physicians in Easton. It was also related by Dr. Traill Green himself at the complimentary dinner given to Dr. Gross on April 10, 1879. At the time—it was in the year 1833—Dr. Gross was conducting experiments on dogs and rabbits, to illustrate the subject of manual strangulation. Many a dog was hanged as a martyr to science. A soldier, a drunken, worthless fellow about Easton, had committed suicide by hanging. Some trouble was experienced in getting him decently buried, but finally he was interred in the cemetery at Easton. In the evening of the same day Traill Green, then a student of medicine at the University of Pennsylvania, was out visiting, when Gross called him to the door and said: "Green, I want that fellow." That night at the hour consecrated to evil spirits, ghosts, ghouls, and hobgoblins, Gross, Traill Green, and another student marched to the cemetery. They took with them a wheelbarrow and a spade. The night was still and very dark. As is usually the case with paupers and unclaimed dead, the man had been buried in a remote corner of the potter's field, where the soil was rough and undulating. They immediately set to work to unearth the coffin. They had not proceeded very far, however, before they were forced to desist. The spade made so much noise in the gravel that they were afraid some one would hear them. Gross said: "Green, we had better quit or we'll get caught." So they gave it up, refilled the grave and left. Several days later a brother of the deceased soldier met Traill Green in the street and said: "Doctor, I believe you got my brother's body." Green replied with the evasive answer, "You can believe what you please." Thus the incident was closed.

Gross longed to qualify himself as a teacher of anatomy. In the spring of 1833 he made known his wishes to Dr. John Eberle, one of his old college preceptors, then a professor in the Medical College of Ohio, at Cincinnati. The result was that he was soon appointed Demonstrator of Anatomy in that institution—the Medical College of Ohio. Accordingly in October, 1833, after a residence of three and one-half years in Easton, he removed to Cincinnati, the "Queen City of the West," to assume his anatomical duties there. He held the position for only two sessions, 1833 to 1835. In 1835 the Medical Department of the Cincinnati College was organized, with a chair of Pathological Anatomy, and to this chair he was unanimously appointed by the trustees. Here he delivered the first systematic course of lectures on morbid anatomy ever given in the United States.

In 1839 Gross was appointed Professor of Medicine in the University of Virginia. A short time previously he had been offered the chair of anatomy in the University of Louisiana. Both of these offers were promptly declined, but in the spring of 1840 he accepted the professorship of surgery in the Louisville Medical Institute, afterwards the University of Louisville. In the following October (1840) he removed from Cincinnati to Kentucky, to inaugurate his work as Professor of Surgery in the University of Louisville.[5]

Gross remained at Louisville for sixteen years, from October, 1840, to September, 1856, with the exception of the winter of 1850-1851, which he spent in New York, as the successor of Dr. Valentine Mott in the chair of Surgery in the University of that city. Shortly after the close of the session, Gross left New York and returned to Louisville.

In 1855 Gross was solicited to allow his name to be proposed as a candidate for the chair of Surgery in the University of Pennsylvania. Various reasons, however, induced him to decline this offer. Early in May, 1856, he was unanimously elected Professor of Surgery in the Jefferson Medical College, from which institution he had been graduated at the age of twenty-three years. This call he could not refuse; so, late in September of the same year (1856), he removed with his family to Philadelphia, where he spent the remainder of his life. He succeeded Dr. Thomas Dent Mütter in the faculty of his Alma Mater, and held the chair from 1856 to 1882, a period of twenty-six years.

BOOKS AND PUBLICATIONS.

Long before Gross finished his student course of studies in Jefferson Medical College, he had determined to undertake the translation of some French work as soon as he should receive his degree. He already had made a selection of Edwards's Manual of Surgical Anatomy, but a few days before he thought of beginning, he found, much to his chagrin and disappointment, that he had been forestalled in his contem-

[5] The following letter from Dr. E. O. Smith, secretary of the faculty of the Ohio-Miami Medical College of the University of Cincinnati, adds some light to this early history:

CINCINNATI, Ohio, January 5, 1912.

Dr. C. W. G. Rohrer, 114 W. Franklin St., Baltimore, Md.

DEAR DOCTOR: Your communication was received yesterday and I have found the following information.

In 1833, through the influence of Dr. John Eberle, Professor of Materia Medica in the Medical College of Ohio, Dr. Samuel D. Gross was appointed demonstrator of Anatomy in that school. In 1835, when Daniel Drake founded the Medical Department of the Cincinnati College, Gross was made Professor of Pathological Anatomy and remained with that school until it closed in 1839. In 1840 he became Professor of Surgery in the Louisville Medical Institute, which position he held for sixteen years. I cannot send you catalogues confirming the above statements as we have no duplicates and the only picture we have of Dr. Gross is framed with a group of other early teachers and of course you can easily see that it would be impossible to send it. However, the statements made are authentic and you can use them in your paper.

Trusting that this is the information that you desire, I am,

Respectfully yours,

(Signed) E. O. SMITH,
Secretary of Faculty.

plated task by Mr. Coulson of London. While debating in his own mind what to do next, he had placed in his hands a French work on anatomy—Bayle and Hollard's General Anatomy. Within a year after his graduation he not only translated this book, but also three additional foreign works—Hatin's Manual of Obstetrics, Hildenbrand on Typhus Fever, and Tavernier's Operative Surgery. He completed his first translation, Bayle and Hollard's General Anatomy, in two months. It formed an octavo volume of about three hundred pages, and the edition numbered two thousand copies. The publisher, Mr. John Grigg of Philadelphia, paid him two hundred dollars for it. In the opening paragraph of his preface Gross first comments upon the newness of this branch of anatomy and then pays a tribute to Bichat. He says:

> General Anatomy is a science of comparatively modern date; and, like every other great and important improvement, it has gradually arrived at its present degree of perfection. To Bichat, no doubt, is due the honor of having first established this branch of anatomy into a science, and the work which he has left us upon this subject is at once an imperishable monument of his great talents and of his ingenious and profound researches.[6]

His second translation was another French work—Hatin's Manual of Obstetrics—a small practical treatise of 166 pages and an appendix. The latter, consisting of 18 pages, contains Magendie's celebrated paper on the cephalo-spinal fluid, which was translated by Dr. Joseph Gardner, a fellow-graduate of Gross. This translation was completed in three weeks, and was also published by Mr. Grigg, who paid Gross the munificent sum of seventy-five dollars.

The third work translated by Gross was Hildenbrand on Typhus Fever. At that time typhus fever, variously called "ship fever" or "jail fever," was a deadly and widely prevalent disease. This little German book was much celebrated in its day. The translation was published by Mr. Elam Bliss of New York, in the winter of 1829. The volume of 180 pages was completed in two months and Gross received one hundred and seventy-five dollars for it. It is interesting to observe that 1829, the year it was published, is the year in which Louis of Paris coined the name "typhoid fever."

It is manifestly evident that Hildenbrand, writing in 1809, must have recognized typhoid fever, and described it under the name of nervous or non-contagious fever. His book contains twelve sections or chapters, and he writes, Section I, p. 9:

> It (the contagious typhus) is distinguished from the pure nervous and asthenic fevers, properly so called, in this, that, although these fevers are ushered in with true vital debility and the ordinary nervous symptoms, they are not contagious; and the affected nervous system manifests only some particular signs of this contagion, as for instance, the stupor and some others which we shall hereafter describe when speaking of the course of typhus. The exanthemata, perhaps, also establish some difference, as well as the periodical exacerbations, which are more peculiar to the simple nervous fevers.

Section II is very interesting, and is entitled "On the Antiquity and History of Typhus, and of Its Effects Upon the Human Race."

Section IV is devoted to the contagious typhus. Its full caption is "Of the Simple Regular Typhus, Communicated by Contagion." In contrast to Section IV is Section XII, entitled "General Observations on the Originary Typhus." In Section XII, page 173, the author says:

> It (the originary typhus) is distinguished from the simple nervous and non-contagious fever, in this, that in the latter, the vertiginous stupor and the catharrhal symptoms are completely wanting; while the other symptoms, such as the subsultus tendinum, the convulsions, the cramps and the general erethism of the body, are greatly aggravated. The periodical exacerbations, whether quotidian, or tertian, are likewise more peculiar to the simple nervous and non-contagious fevers.

The fourth translation by Gross, and the last he ever attempted, was another French book, Tavernier's Operative Surgery. The first volume was translated in less than three months. Tavernier's work of two octavo volumes of nearly five hundred pages each, was the first treatise on operative surgery ever published in the United States.[7] The publisher, Mr. Grigg, paid Gross four hundred dollars for his labors. Volume II, entitled Clinical Surgery, was not translated by him.

Before passing from these four translations to his original works, I wish to call brief attention to the rapidity and magnitude of the task accomplished by the young physician. It was his custom to translate from twenty to twenty-five pages a day, no matter what might be his other engagements. The average French or German student of the present generation would be in imminent danger of heart failure if his teacher were to assign him so stupendous a task.

Having completed the four above-mentioned translations, Gross set to work forthwith upon the composition of his first original work. This book, written with a facile pen, was entitled "The Anatomy, Physiology, and Diseases of the Bones and Joints." It consists of an octavo volume of nearly four hundred pages, and was finished in the space of little more than three months. The work was issued in the autumn of 1830, by Mr. Grigg. The preface is dated "Easton, July, 1830."

When he wrote this book he was but twenty-five years of age, and he seems to have had some misgivings as to the reception which would probably be accorded it because of his youth and inexperience. On page iv of the Preface, Gross states:

> "If," to use the language of an eloquent writer,[8] "any one should conceive the present undertaking to be above the capacity

[6] I wish to call attention to the fact that in Bayle and Hollard's General Anatomy each subject closes with a paragraph on pathological anatomy and a complete bibliography. There is also an Appendix, containing an account of four so-called Accidental Tissues: a. Tuberculous productions. b. Scirrhus. c. Encephaloid or cerebriform cancer. d. The melanotic substance.

[7] This surgery is preceded by an Introduction consisting of twenty-five closely printed pages, which gives a concise history of surgery. In Chapter IV, Sec. 4, p. 308, occurs a brief account of Sir Astley Cooper's famous operation of ligating the abdominal aorta.

[8] Richerand. Preface to his Elements of Physiology.

of my age, I will say, even at the risk of a paradox, that young men are perhaps best fitted to compose elementary works; because the difficulties which they have encountered in their studies, as well as the steps which they have taken to overcome them, are still fresh in their memory."

However, this early effort was well received, and two thousand copies were exhausted in less than four years. A second edition was not issued. The author states that he never received a cent of remuneration for this book.

Dr. Gross was the first to describe the use of adhesive plaster in the treatment of fractures. This description (Chap. II, Art. II, under the caption, "Treatment of Complicated Fractures") reads as follows:

If the bone be broken into several pieces, and any of them are completely detached, or so loose as to render their union highly improbable, all such pieces ought to be carefully removed; after which the edges of the wound should be slightly approximated, and kept in this position by a few short strips of adhesive plaster. The limb should be placed upon a pillow and surrounded with the bandage of Scultetus, and every care taken to obviate and remove inflammation. When the wound suppurates, it should be frequently dressed with some digestive ointment, or soft emollient poultices, as circumstances may require, care being taken that at each application of them the fracture be disturbed as little as possible. As soon as the inflammation has subsided, and the parts begin to heal, the ends of the fragments should be brought into contact, and be maintained in apposition by appropriate splints and dressings..... In complicated fractures of the leg, it not unfrequently happens that the soft parts about the ankle are so much contused, or otherwise injured, as to render it impossible to employ the usual extending bands. When this is found to be the case, the difficulty may usually be remedied by applying along each side of the leg, as high up as the seat of the fracture will admit, a piece of strong muslin, about two feet and a half in length, two inches and a half in width, and spread at one of its extremities with adhesive plaster. The part which is applied upon the limb should be confined by three or four circular strips, so as to keep it firmly in its place, and equalize the extending power. The free extremities of the extending bands should then be tied under the sole of the foot, and be secured to the block or bar which connects the lower ends of the splints. This mode of making extension, for which we are indebted to the ingenuity of my friend and preceptor, Dr. Swift, of this place (Easton), will, I am fully persuaded, be found highly useful in practice, and satisfactorily obviate the inconveniences to which I have just alluded.

Apropos of the four translations and the book on the Bones and Joints, Gross thus writes in his Autobiography (p. 43):

All these works were published in about eighteen months after I took my degree. The different translations and the book on the Bones and Joints formed nearly fifteen hundred pages octavo. In addition to this, I assisted the late Dr. Godman in translating the Duke of Saxe-Weimar's Travels in the United States, published soon afterwards by Carey and Lea. This work was written in German, and I completed about two hundred pages of it in less, I think, than a fortnight.... My practice during this period was, of course, limited; I went little into society and took hardly any recreation. Depriving myself of pleasure and amusement, I devoted my time to my task, thus literally verifying the saying of the Roman, *Nulla dies sine linea*. I labored day and night under the stimulus both of ambition and of poverty.

As has been stated in a previous paragraph, in the month of April, 1830, Gross removed from Philadelphia to Easton. While residing there he spent all his leisure during the summer months upon the composition of a work on Descriptive Anatomy. In it he makes the effort for the first time in English to change the nomenclature of anatomy from Latin into English. This book, however, was never entirely completed and never published.

Next, as a result of four years' study and teaching, his Elements of Pathological Anatomy was published. The work was founded upon knowledge derived from dissections made during his occupancy of the chair of pathological anatomy in the Cincinnati Medical College, from an elaborate course of reading, and from numerous visits to the slaughter-houses of Cincinnati. It was issued in 1839, in two octavo volumes of more than five hundred pages each. The book was illustrated by numerous wood-cuts and several colored engravings, and was the first systematic work upon the subject ever published in the United States, or, indeed, in the English language.

It is true, as the worthy president of this society, Dr. Henry Barton Jacobs, told us in his interesting disquisition on "The Gold-headed Cane," that Dr. Matthew Baillie of London published a little book on pathology as early as 1793, but Dr. Baillie's book does not purport to be a complete treatise. It is entitled, "On the Morbid Anatomy of Some of the Most Important Parts of the Human Body."

In Volume II (pp. 458-463), Gross gives an account of a number of dissections of specimens of false conceptions or uterine moles—the first account of them in the English language. His examinations of the prostate gland have also been fully quoted by Sir Henry Thompson and others.

A second edition of the Elements of Pathological Anatomy, greatly enlarged and thoroughly revised, was issued in 1845. It consists of one large octavo volume of eight hundred and twenty-two pages, illustrated by colored engravings and two hundred and fifty wood-cuts. It contains full marginal references, which greatly enhance its value. A copy of the second edition was a favorite book of Professor Rudolph Virchow. Speaking of the Elements, Dr. J. M. DaCosta, in his Biographical Sketch of Dr. Gross, says:

It is a mine of learning, and its extended references make it valuable to this day. Its merits have been fully recognized abroad; and on no occasion more flatteringly than when the great pathologist, Virchow, at a dinner given to Dr. Gross at Berlin in 1868, complimented him publically on being the author, and, pointing to the volume, which he laid upon the table, gracefully acknowledged the pleasure and instruction which he had often gained from it.

A third and last edition of this work appeared in 1857, from the press of Blanchard and Lea. It was in some degree an abridgment of the second edition, and yet it comprised a very good outline of the existing state of the science.

Before leaving the subject of pathological anatomy and passing on to the next, I wish to quote a few sentences relating thereto, written by Gross in February, 1870, as follows:

A knowledge of pathological anatomy is the very basis of diagnosis; and when it is considered how important it is that a physician should be able to determine the nature of a disease before he institutes his treatment, it is not a little surprising that this

department of medicine should be taught in so few of our medical schools. This omission is one of the crying sins of the present day. Everything, however irrelevant and useless, is taught to the exclusion of morbid anatomy. I only wish that every medical college in the country were compelled to introduce it into its curriculum of studies. To make room for it we might well dispense with some of the useless teachings in chemistry, materia medica, physiology, and even midwifery, so characteristic of the present day.

In 1842 Dr. Gross edited, with copious notes and additions, the American publication of Robert Liston's Elements of Surgery, a famous work in its day. Liston's book had a perfect right to be good, because its author was ably seconded in his anatomical and surgical investigations by one Ben Crouch—probably the most celebrated resurrectionist or body-snatcher of all time.

In the spring of 1841, Dr. Gross commenced his investigations on the nature and treatment of wounds of the intestines. The experiments, upwards of seventy in number, were performed exclusively on dogs, and were continued with various intermissions for more than two years, culminating in the publication, in 1843, of a work entitled, "Wounds of the Intestines."

Blanchard and Lea, in 1851, published his work entitled, "A Practical Treatise on the Diseases, Injuries and Malformations of the Urinary Bladder, the Prostate Gland, and the Urethra." This work was at once accepted as authoritative upon these subjects. A second edition, greatly enlarged and improved, was issued in 1855. It forms a closely-printed octavo volume of nine hundred and twenty-five pages, illustrated by one hundred and eighty-four wood-cuts. Perhaps the best-known of these wood-cuts are those (pp. 70 and 71) illustrating the size and form of the human prostate gland in seven subjects of different ages. In an appendix of twenty-nine closely-printed pages is the first and only attempt ever made by any writer to furnish a complete account of the prevalence of stone in the bladder and of calculous disorders in the United States, Canada, Nova Scotia, Europe, and other countries. A third and last edition of this work was issued in September, 1876, under the able editorship of Dr. Gross's son, Dr. Samuel W. Gross.

In 1854, Dr. Gross's work, "A Practical Treatise on Foreign Bodies in the Air-Passages," was also issued from the press of Blanchard and Lea. He was occupied upwards of two years in its composition. It consists of an octavo volume of four hundred and sixty-eight pages, illustrated by fifty-nine engravings on wood. As the author himself states: "It was the first attempt to systematize our knowledge upon the subject, and the work is therefore, strictly speaking, a pioneer work." This work has long been out of print, and has never been reissued. The late Sir Morrell Mackenzie, the highest authority on the subject in Europe, in speaking of this work nearly thirty years after its publication, makes the following remark: "This invaluable essay gives full reports of two hundred cases, and is so complete that it is doubtful whether it will ever be improved upon; indeed, the excellent articles of Bourdillat and Kühn, subsequently published, the former based on three hundred, and the latter on three hundred and seventy-four cases, only confirm the conclusions previously arrived at by Gross."[9]

Several years before Dr. Gross left Kentucky he had commenced the composition of his System of Surgery. He states that he had determined to do his best to make it, if possible, the most elaborate if not the most complete treatise in the English language. Early in the spring of 1859 the manuscript was submitted to the publishers, Messrs. Blanchard and Lea. The preface is dated Jefferson Medical College, Philadelphia, July 8, 1859. The work consists of two portly octavo volumes, numbering in the aggregate two thousand three hundred and sixty pages, and illustrated by nine hundred and thirty-six engravings on wood. The edition comprised two thousand copies. The full title of the work is:

A
SYSTEM OF SURGERY:
PATHOLOGICAL, DIAGNOSTIC, THERAPEUTIC,
AND OPERATIVE.
BY
SAMUEL D. GROSS, M. D.,
Professor of Surgery in the Jefferson Medical College of Philadelphia;
Member of the American Philosophical Society; Fellow of the College of Physicians of Philadelphia;
Corresponding Member of the New York Academy of Medicine, and of the
Imperial Royal Medical Society of Vienna;
Author of a Treatise on the Urinary Organs, etc.
ILLUSTRATED BY
NINE HUNDRED AND THIRTY-SIX ENGRAVINGS.
IN TWO VOLUMES.
PHILADELPHIA:
BLANCHARD AND LEA.
1859.

The following inscription adorns the dedicatory page of Dr. Gross's System of Surgery:

TO
THE NUMEROUS PUPILS
WHO, DURING THE LAST QUARTER OF A CENTURY,
HAVE ATTENDED HIS LECTURES,
AND WHO ARE NOW SETTLED IN EVERY SECTION OF THE UNITED STATES
IN THE
HONORABLE PURSUIT OF THEIR PROFESSION,
THESE VOLUMES,
DESIGNED TO ILLUSTRATE ONE OF THE MOST IMPORTANT AND VALUABLE BRANCHES OF THE HEALING ART,
ARE RESPECTFULLY AND AFFECTIONATELY INSCRIBED
BY THEIR FRIEND,
THE AUTHOR.

The comprehensiveness of this system is indicated in one sentence on the first page of the preface. Dr. Gross writes:

[9] Sir Morrell Mackenzie: Diseases of the Throat and Nose, vol. I, p. 450. Philadelphia, 1880.

"My aim has been to embrace the whole domain of surgery, and to allot to every subject its legitimate claim to notice in the great family of external diseases and accidents."

In Volume I (pp. 588-589), he discourses eloquently on the "Qualifications of a Surgeon." The four paragraphs could be read with advantage by every medical student. He sums up the situation as follows:

> Celsus, long ago, happily defined the qualities which constitute a good operator. He should possess, says the illustrious Roman, a firm and steady hand, a keen eye, and the most unflinching courage, which can disregard alike the sight of blood and the cries of the patient.

Some of us, I am sure, are also reminded of Sir John Bell's ideal of the qualities necessary in a truly great surgeon—"The brain of an Apollo, the heart of a lion, the eye of an eagle, and the hand of a woman."

The Gross System of Surgery passed through six editions, each being a decided improvement upon its predecessor. The sixth and last edition was issued in 1882, just seventeen months before the death of its venerable author.

At the outbreak of the Civil War, Dr. Gross wrote a brief Manual of Military Surgery. It was composed in nine days, and published in a fortnight from the time of its inception. Under the care of Messrs. J. B. Lippincott and Company, it passed through two editions of 2,000 copies each. It was republished at Richmond, Virginia, and was extensively used by the surgeons of both armies. In 1874, it was translated into Japanese and published at Tokio, Japan. The first edition bears the date of 1861; the second edition, 1862.[10]

In 1861 Dr. Gross wrote, or rather edited, a work entitled, "Lives of Eminent American Physicians and Surgeons of the Nineteenth Century." It is an octavo volume of upwards of eight hundred pages, now exceedingly scarce. To this work he contributed three sketches on Dr. Ephraim McDowell, Dr. Daniel Drake, and Dr. John Syng Dorsey. This book is the third publication on American medical biography. The first, issued in 1828, was edited by Dr. James Thacher of Massachusetts, and the second, edited by the late Dr. Stephen W. Williams, also of Massachusetts, appeared in 1845. Dr. Gross's book contains a full and complete account of the life and work of thirty-two eminent American physicians and surgeons, now of a by-gone medical epoch.

A few years later he wrote a valuable work entitled, "A Full Account of Special Surgery on Diseases and Injuries of Particular Organs, Textures, and Regions." A fifth edition of this work was issued in 1872.

In 1876 he wrote the section on Surgery, in the centennial volume entitled, "A Century of American Medicine, 1776-1876." It is a masterly article consisting of one hundred pages, originally contributed to The American Journal of the Medical Sciences.

Dr. Gross delivered the first anniversary address before the Philadelphia Academy of Surgery in 1881. It was a memoir of John Hunter, with the title of John Hunter and His Pupils, later published in book form. In the preface he states: "In assuming this duty I selected for my theme the life, character, and services of the founder of scientific surgery." The portrait which fronts this little volume on John Hunter is the familiar one from Sharp's steel engraving of Sir Joshua Reynold's celebrated painting. The text itself has been liberally quoted by Dr. Mather, in his excellent book entitled, "Two Great Scotsmen—William and John Hunter."

On February 14, 1884, Dr. Gross made the final entry in his Autobiography, a handsome two-volume work which has come down to us as a priceless heritage. The Autobiography was edited by his two sons—the late Dr. Samuel W. Gross and the Hon. A. Haller Gross of the Philadelphia Bar. Its full title is: "Autobiography of Samuel D. Gross, M. D., with Reminiscences of his Times and Contemporaries." It was begun about fifteen years prior to the death of its distinguished author and published in 1887, three years subsequently. In the opening paragraph, Dr. Gross states his reasons for writing it in the following words:

> It is my wish to write a sketch of my life for the gratification of my children and grandchildren, and for the benefit of such members of my profession as may feel an interest in me from my long connection with it. Possibly some good may grow out of such a labor, by stimulating the ambition of those who may come after me to work for the advancement of science and the amelioration of human suffering. The devotion which I have shown to my profession may, perhaps, exert a salutary influence upon the conduct of young physicians, and thus serve to inspire them with a desire to excel in good deeds.

The Autobiography is preceded by a Memoir of Dr. Gross by the late Dr. Austin Flint, Sr., a former colleague and lifelong friend. This Memoir is an excellent portrayal of the life and labors of one of the foremost men of his day—one who is declared to have been "perhaps the most eminent exponent of medical science that America has yet produced."

CONTRIBUTIONS TO MEDICAL SCIENCE.

In addition to his published works, Dr. Gross wrote numerous important journal articles, which cover a wide range of subjects. The principal titles, arranged in chronological order, are as follows:

Report on Kentucky Surgery, 1851.

An Account of a Case of Axillary Aneurism, 1852.

On the Diseases and Operations on the Jaws, 1852.

A Short Account of the Use of Adhesive Plaster in the Treatment of Fractures, 1852.

A Discourse upon the Life and Character of the late Dr. Drake, 1853.

Results of Surgical Operations in Malignant Diseases, 1853.

Causes which Retard the Progress of American Medical Literature, 1856.

August Gottlieb Richter: his Works and his Contemporaries, 1856.

Hypertrophy of the Gums, 1856.

Report of a Case of Gunshot Wound of the Neck, 1856.

Necrological Notice of the late Dr. John K. Mitchell, 1858.

[10] Another favorite volume with the surgeons of both contending armies was Dr. Julian J. Chisolm's excellent "Manual of Military Surgery for the Use of Surgeons in the Confederate Army, 1861."

Nature and Treatment of Tuberculosis of the Hip-joint, 1858.

Sketch of the Life and Services of Ambroise Paré, 1860.

An Account of a Remarkable Case of Melanosis, or Black Cancer, 1860.

Practical Observations on the Nature and Treatment of Prostatorrhoea, 1860.

Brunonianism, Toddism, and other Isms, 1861.

Necrological Notice of Jedediah Cobb, M. D., 1861.

Biographical Sketch of Charles Wilkins Short, M. D., 1865.

Then and Now: Advances in Medical Science in the Past Forty Years, 1867.

The Live Physician, 1868.

A Memoir of Valentine Mott, M. D., 1868.

A New Method of Appointing Medical Witnesses as Experts in Cases involving Medico-Legal Considerations, 1868.

A Memoir of Robley Dunglison, M. D., 1869.

Training of Nurses, 1869.

Nature's Voice in Disease and Convalescence, 1870.

Syphilis in its Relation to the National Health, 1874.

The Factors of Disease and Death after Injuries, Parturition, and Surgical Operations, 1874.

Bloodletting Considered as a Therapeutic Agent; or, One of the Lost Arts, 1875.

The Glories and Hardships of the Medical Life, 1875.

The Proximate Cause of Pain, 1877.

A Memoir of Dr. Isaac Hays, 1879.

The Social Position of the Doctor, 1880.

Value of Early Operations in Morbid Growths, 1883.

The Importance of Having Trained Nurses for the Smaller Towns and Rural Districts, and the Proper Method of Securing Them, 1883.

Obituary Notice of Dr. J. Marion Sims, 1883.

Wounds of the Intestines, 1884.

Lacerations of the Female Sexual Organs Consequent upon Parturition, 1884.

I cannot attempt to describe all of these thirty-seven papers and journal articles, but two or three notes may add to their interest. For example, it was in his elaborate "Report on Kentucky Surgery," prepared in 1851, that Dr. Gross first established the fact that the late Dr. Ephraim McDowell of Danville, in that State, was justly entitled to the honor of being the father of ovariotomy.

In the closing paragraph of his paper on the "Causes which Retard the Progress of American Medical Literature," read before the American Medical Association in 1856, Dr. Gross embodied three resolutions:

Resolved, That this Association earnestly and respectfully recommend, first, the universal adoption, whenever practicable, by our schools, of American works as text-books for their pupils; secondly, the discontinuance of the practice of editing foreign writings; thirdly, a more independent course of the medical periodical press towards foreign productions, and a more liberal one towards American; and, fourthly, a better and more efficient employment of the facts which are continually furnished by our public institutions for the elucidation of the nature of diseases and accidents, and, indirectly, for the formation of an original, a vigorous, and an independent national medical literature.

Resolved, That we venerate the writings of the great medical men, past and present, of our country, and that we consider them as an important element of our professional and national glory.

Resolved, That we shall always hail with pleasure any useful and valuable works emanating from the English press, and that we shall always extend to them a cordial welcome as books of reference, to acquaint us with the progress of legitimate medicine abroad, and to enlighten us in regard to any new facts of which they may be the repositories.

Dr. Gross also gave a number of special lectures and addresses, each being a model of its kind. These may be summarized as follows:

Inaugural Address, Jefferson Medical College, 1856.

Valedictory Address, Jefferson Medical College, 1860.

Address before the Alumni Association, Jefferson Medical College, 1871.

Address before the Medical Society of the State of Pennsylvania, 1871.

History of American Medical Literature from 1776 to the Present Time, 1875.

Address delivered before the Kentucky State Medical Society, 1879.

Valedictory Address, Bellevue Hospital Medical College, 1882.

Address of Welcome before the National Association for the Protection of the Insane and the Prevention of Insanity, 1883.

His Inaugural Address delivered at the opening of the 1856-1857 session of the Jefferson Medical College was a praiseworthy effort. In it he feelingly refers to his regret at leaving Kentucky. He says:

It was pleasant to dwell in the land of Boone, of Clay, and of Crittenden; to behold its fertile fields, its majestic forests, and its beautiful streams; and to associate with its refined, cultivated, generous-hearted, and chivalric people. It was there that I had hoped to spend the remainder of my days upon objects calculated to promote the honor and welfare of its noble profession, and finally to mingle my dust with the dust and ashes of the sons and daughters of Kentucky. But destiny has decreed otherwise. A change has come over my life. I stand this evening in the presence of a new people, a stranger in a strange place, and a candidate for new favors.

He concludes his address in the following words:

Whatever of life, and of health, and of strength remains to me, I hereby, in the presence of Almighty God and of this large assemblage, dedicate to the cause of my Alma Mater, to the interests of Medical Science, and to the good of my fellow-creatures.

I shall pass in brief review but one other of these eight lectures and addresses. It is the address delivered before the Kentucky State Medical Society at its meeting at Danville, May 14, 1879, at the dedication of the monument erected in memory of Ephraim McDowell, the "Father of Ovariotomy."[11] It was a masterly effort, Dr. Gross being at his best.

At the close of the dedicatory services the door-knocker of Dr. McDowell's house was presented to Dr. Gross by Dr. Richard O. Cowling, president of the Kentucky State Medical Society. In presenting it, Dr. Cowling said, in part:

I would that the magician's wand were granted me awhile to weave a fitting legend around this door-knocker, which comes from McDowell to you, Dr. Gross. There is much in the emblem. No one knows better than you how good and how great was the man of whom it speaks. It will tell of many a summons upon

[11] This splendid dedicatory address is given in full in Mrs. Ridenbaugh's excellent Biography of Dr. Ephraim McDowell. It fills sixty-five pages of the book.

mercy's mission which did not sound in vain. Ofttimes has it roused to action one whose deeds have filled the world with fame. A sentinel, it stood at the doorway of a happy and an honorable home, whose master, as he had bravely answered its signals to duty here below, so when the greater summons came, as trustfully answered that, and laid down a stainless life.

It belongs by right to you, Dr. Gross. This household genius passes most fittingly from the dearest of Kentucky's dead surgeons to the most beloved of her living sons in medicine. She will ever claim you as her son, and will look with jealous eye upon those who would wean you from her dear affection.

And as this emblem which now is given to you hangs no longer in a Kentucky doorway, by this token you shall know that all Kentucky doorways are open at your approach. By the relief your skill has wrought; by the griefs your great heart has healed; by the sunshine you have thrown across her threshold; by the honor your fame has brought her; by the fountains of your wisdom at which your loving children within her borders have drunk, the people of Kentucky shall ever open to you their hearts and homes.

Dr. Gross was much overcome by this mark of approbation, coming from the Kentucky State Medical Society, and by Dr. Cowling's well-chosen words. He replied, in part:

I take this emblem now offered to me as the most valued gift of my life. It shall be received into my home as a household god, environed by all the memories of goodness and greatness to which your speaker has referred, and above all recalling this scene. Dying I shall bequeath it, among my most important possessions, to the family that I may leave, or in failure of that, to be preserved in the archives of some society.

Five years later, when Dr. Gross died, Dr. McDowell's door-knocker was presented to the Philadelphia Academy of Surgery. It was subsequently transferred to the museum of the College of Physicians of Philadelphia, where it is now tenderly treasured.

I made an honest effort to borrow Dr. McDowell's door-knocker and bring it to Baltimore, to show at this meeting; but I did not succeed.[12]

ACHIEVEMENTS IN MEDICINE AND SURGERY.

A faithful record of the achievements of Dr. Gross in medicine and surgery would carry us far beyond the limits of the present paper. He usually spoke of himself as a physician rather than a surgeon. His most important original contributions to medicine and surgery, apart from authorship, may thus be enumerated:

Eperiments on dogs and rabbits, to illustrate the subject of manual strangulation.

Experiments upon secretion, to ascertain the rapid transit of certain articles, when taken into the stomach, through the blood by the kidneys.

Weights and measurements of healthy organs.

Experiments on the nature and treatment of wounds of the intestines.

Dissections of specimens of false conceptions, or uterine moles.

Observations on the temperature of venous blood in healthy persons of both sexes.

Deep stitches in wounds of the wall of the abdomen, to prevent hernia or protrusion of the bowel after recovery.

The invention of an enterotome for the treatment of artificial anus.

A tracheotomy forceps, for the extraction of foreign bodies from the air-passages.

Wiring the ends of the bones in dislocations of the sterno-clavicular and acromio-clavicular joints.

Blood catheter, an instrument for drawing off the urine, when mixed with blood.

An arterial compressor—a peculiar pair of forceps—for arresting hemorrhage in deep-seated vessels.

A tourniquet, or compressor, for compressing the vessels of the extremities in amputation.

An instrument for extracting foreign bodies from the nose and ear, found in nearly every pocket case in the country.

Modification of Pirogoff's amputation at the ankle joint, unjustly ascribed to Dr. Quimby, of Jersey City.

Laparotomy in rupture of the bladder.

Direct operation for hernia by suturing the pillars of the ring.

Mode of operating for inverted toe-nail.

Apparatus for the transfusion of blood.

First account of prostatorrhoea.

Description of a new form of neuralgia of the jaws in old persons.

Pododynia, a disease of the foot, first described by him.

He was the first to describe the use of adhesive plaster as a means of making extension in the treatment of fractures of the lower extremity.

He was the first to make it a practice to administer morphine and quinine in large doses.

He was the first to suggest the use of ergot in the treatment of diabetes.

He suggested a new method of treating ganglia of the hand and foot by subcutaneous division of the cyst.

He was the first to practice putting a patient under the full influence of opium, immediately after evacuating a chronic abscess.

He early taught the doctrine of the inflammatory origin and vitality of tubercle of the lungs and other structures.

He was the first to teach that amputation in senile gangrene should be performed at a great distance from the affected parts.

He was the first to sew together the ends of an accidentally divided tendon of the hand.

For many years he taught that scrofulous diseases are nothing but remote forms of syphilis. To-day, however, scrofula is known to be tuberculous in character.

MISCELLANEOUS.

Among his other services to the profession and to humanity at large, the following are deserving of mention. While residing at Easton, in 1832, the great scourge of epidemic Asiatic cholera visited the United States. The disease first appeared in Canada, and then in New York. Early in July it broke out with great virulence in New York City. Great excitement prevailed throughout the entire Atlantic seaboard. Easton, only eighty miles off, participated in the alarm. At a meeting of the town council held on the 19th of July, 1832, Dr. Gross was appointed to visit New York for the purpose of investigating the disease. The situation was one well calcu-

[12] The following note from Dr. Keen explains the situation.

1729 CHESTNUT STREET, PHILADELPHIA,
January 2, 1912.

MY DEAR DR. ROHRER: I have your letter of the 1st. Dr. Ephraim McDowell's door-knocker is in the Museum of the College of Physicians. I presume that your photographer would be allowed to photograph it, but no permission I am sure would be granted to take this relic out of the Museum itself.

Yours very truly,
(Signed) W. W. KEEN.

lated to try the mettle of the young physician. But he responded heroically to the call of duty and of humanity. I shall repeat briefly the whole story, in the language of Dr. W. W. Keen:[13]

> In 1832, that most dreaded of all scourges, Asiatic cholera, for the first time broke out all over this country with the greatest virulence. Easton was only eighty miles from New York and the citizens, in terror lest the dread disease would reach their own town, appointed a young, intrepid surgeon to visit New York and learn what he could do for their benefit. When others were fleeing in frightened thousands from the pestilence, Gross bravely went directly into the very midst of it, reaching New York when the epidemic was at its very height. In that, then small and half-depopulated, town 385 persons died on the very day of his arrival —and he stayed there a week in a hot July, visiting only its hospitals and its charnel-houses. What call you that but the highest type of bravery?—a bravery which Norfolk and Mobile and Memphis and New Orleans have since seen repeated by scores of courageous physicians ready to sacrifice their lives for their fellowmen with no blare of trumpets, no roar of cannon, no cheer of troops, no plaudits of the press! No battlefield ever saw greater heroes; no country, braver men!

Dr. Gross possessed great powers of organization. He was one of the founders of the Kentucky State Medical Society, and of the Medical Jurisprudence Society of Philadelphia. In the autumn of 1857 he founded, along with Dr. J. M. Da Costa, the Philadelphia Pathological Society. He was the originator of the Philadelphia Academy of Surgery, which was founded in 1879; also the American Surgical Association, instituted in 1880. For this reason we speak of him as the "father of the American Surgical Association," just as we speak of the late Dr. Nathan Smith Davis as the "father of the American Medical Association."

Degrees and Honors.

In addition to the M. D. degree, which Dr. Gross received from Jefferson Medical College in March, 1828, and certificates of proficiency from the several preparatory schools in which he received his academic training, he was the recipient of several honorary degrees from universities at home and abroad. He was made an LL. D. by the Jefferson College of Canonsburg, Pennsylvania, in 1861. In 1872 the University of Oxford conferred upon him the degree of D. C. L., the University of Cambridge the degree of LL. D., in 1880, and the University of Edinburgh and the University of Pennsylvania conferred the same degree, *in absentia*, in April and May, 1884.

He was a member of a score of American medical and scientific societies, and honorary member of nearly a dozen similar European societies. These include honorary membership in the Pathological Society of London, a justly deserved honor, as Dr. Gross was the first regular teacher of pathological anatomy in the United States.

Private Life.

In private life no man was more beloved, whether in his ideal and hospitable home or in the ever-widening circle of his friends and acquaintances. To quote the language of Dr. Austin Flint, Sr.:[14]

> His home was open to all who had any claim upon his attentions. He was considerate and generous alike to the guest who was renowned in letters at home and abroad, and to the young physician and the medical student. As has been said by Froude, "Nowhere is a man known better than in his own family. No disguise is possible there; and he whom father and mother, brother and sister love, we may be sure has deserved to be loved." No father was ever kinder, no husband more affectionate.

Dr. Gross believed in early marriages. True to his convictions, in the winter of 1828-29, in Philadelphia, he married the woman of his choice, the widow of Mr. Hugh Dulany. Her maiden name was Louisa Ann Weissell. She was born in Kensington, London, when her parents were on a visit to England. Mrs. Gross had a singularly gifted intellect and was a most brilliant conversationalist. She was of deep religious convictions. She died February 27, 1876.

Of the eight children born to Dr. and Mrs. Gross, three daughters and five sons, three died in infancy and another in her ninth year. The remaining four attained to their majority. These were two daughters and two sons. One son, the late Dr. Samuel Weissell Gross, whom his father declared to be the "greatest of all his works," died of pneumonia on the 16th of April, 1889, in the fulness of his powers as a great surgeon. At the time of his death he held the chair of Principles of Surgery and Clinical Surgery at the Jefferson Medical College, Philadelphia, and was most signally following in the footsteps of his father, for whose great System of Surgery he was engaged in collecting the information for a projected new edition. A daughter, Louisa, the late Mrs. Benjamin F. Horwitz of this city, a brilliant, charming woman and a great musician, died June 1, 1907.

Two of the children of Dr. Gross are still living. They are Mrs. Maria Gross Horwitz, widow of the late Orville Horwitz, and the Hon. A. Haller Gross, of the Philadelphia bar. To the latter I am indebted for many important facts concerning his father's life, and for the handsome autograph portrait. The traits that stand out in Dr. Gross's life were his purity of character, his great decision, his untiring industry, his self-reliance, his freedom from bigotry and superstition, and his manliness. He was a representative man and citizen. Physically, he was a singularly handsome man, six feet two inches in height, weighing 205 pounds.

Summary of Life Work.

In summing up his life-work, we find that it was great in deeds and also great in years. Born in humble circumstances, his early days were spent in a rural community. Constant outdoor exercise, an excellent home training and example, and a wholesome environment enabled the country lad to lay the foundations of that splendid physique which stood him in such good stead when the responsibilities of a most exacting profession weighed so heavily upon his shoulders. From his youth up he was of studious habits and fond of natural history. He was known as a good, moral young man.

[13] Address at the unveiling of the bronze statue of the late Prof. Samuel D. Gross, M. D., May 5, 1897.

[14] Memoir of Dr. Gross, which precedes the Autobiography, pp. XXVIII-XXIX.

As a medical student, both in the private office and in the medical school, he was ever attentive and diligent, earnestly seeking to make the most of his opportunities. He was primarily a pathologist, secondarily a physician and surgeon. He was a living embodiment of the late Hughlings Jackson's statement, "A good physician must be a good pathologist." And as all operators do who achieve real greatness, he entered the surgical arena through the portals of pathology. He was America's first pathologist.

Dr. Gross always thought himself a better physician than surgeon. As a practitioner, he was very successful, and for many years he had an immense family practice. A large share of his consultation work in Philadelphia, Louisville, and Cincinnati was of a strictly medical character. At one time he was extensively engaged in midwifery in connection with family practice. As an accoucheur he never lost but one woman by puerperal fever, and he never had occasion to apply forceps in any case originally under his care.

As a surgeon, Dr. Gross was a conservative and safe operator. Early in his career he was appalled at the sight of blood. But he possessed the staying qualities of a good operator—a steady hand, an unflinching eye, perfect self-control, and a thorough knowledge of relative anatomy. He was also a skillful diagnostician.

He was an original thinker, an inspiring teacher, and a voluminous author. He was an investigator of the highest rank. In the phraseology of Dr. W. W. Keen: "He 'blazed' more than one new 'trail' in the forests of surgical ignorance."

CLOSING YEARS.

On April 10, 1879, a complimentary banquet was given to him at the old St. George Hotel in Philadelphia. It was on the occasion of the fifty-first anniversary of his entrance into the medical profession. It was a memorable gathering, and reference was made to it in the "Remarks of A. Haller Gross at Mr. Potter's[15] luncheon, June 6, 1910," in the following words:

> How well do I recall the occasion, graced as it was by the presence of some of the most distinguished physicians and surgeons of America, who vied one with another in doing honor to my father, and whose burning, eloquent words of welcome and God-speed fill my memory now after the lapse of thirty-one years. I can see Dr. Agnew, the distinguished Professor of Surgery at the University of Pennsylvania, who presided, pinning to the lapel of my father's coat a jeweled badge, presented by the subscribers to the banquet as a testimonial of their affection and esteem, accompanying the act by an exquisite burst of eloquence. And I can recall, as if it were yesterday, a sentence of my father's address—"Oh, for a glance at the profession half a century hence when man, enlightened and refined by education and redeemed from the thraldom of ignorance and superstition, shall reflect more perfectly than he now does the image of his Maker!"

On March 28, 1882, Dr. Gross resigned the chair of surgery in the Jefferson Medical College of Philadelphia, a position which he had filled with signal honor for twenty-six years. Altogether he had been a teacher of medicine and surgery for forty-nine years. His successors to the chair of surgery were his son, Dr. Samuel W. Gross, and Dr. John H. Brinton.[16]

After two years of retirement and failing health, he died, May 6, 1884, at which date he had almost rounded out his seventy-ninth year. A post-mortem examination, conducted by Dr. J. M. Da Costa, showed that Dr. Gross had suffered from marked gastric catarrh. There were irregular thickenings of the mucous membrane of the stomach, and a fatty heart. The right kidney contained a large cyst. The brain weighed forty-eight ounces.

At his own request his body was cremated at Washington, Pennsylvania, in Dr. Lemoyne's crematory, the only one in America at the time. This took place on the 8th of May, and in a little less than two hours and a half all that remained of the "Nestor of American Surgery" were the accustomed seven pounds of ashes. These were placed in an urn, and deposited in Woodlands Cemetery, Philadelphia, next to the coffin of his wife. Upon the urn is the following inscription, written by a former pupil, Dr. D. W. Yandell of Kentucky:

IN MEMORIAM.

WITHIN THIS URN LIE THE ASHES OF

SAMUEL D. GROSS,

A MASTER IN SURGERY.

His life, which neared the extreme limits of the Psalmist, was one unbroken process of laborious years.

He filled chairs in four Medical Colleges in as many States of the Union and added lustre to them all.

He recast Surgical Science, as taught in North America, formulated anew its principles, enlarged its domain, added to its art, and imparted fresh impetus to its study.

He composed many books, and among them

A SYSTEM OF SURGERY,

Which is read in different tongues, wherever the Healing Art is practised.

With a great intellect, carefully trained and balanced, he aimed with undivided zeal at the noble end of lessening human suffering and lengthening human life, and so rose to the highest position yet attained in Science by any of his countrymen.

Resolute in truth, he had no fear; yet he was both tolerant and charitable.

Living in enlightened fellowship with all laborers in the world of Science, he was greatly honored by the learned in foreign lands, and deeply loved at home.

Behind the veil of this life there is a mystery which he penetrated on the

SIXTH DAY OF MAY, 1884.

HIS MEMORY

Shall exhort and his Example shall encourage and persuade those who come after him to emulate deeds which, great in themselves, were all crowned by the milk-white flower of

A STAINLESS LIFE.

[15] Hon. William Potter, president of the Board of Trustees of Jefferson Medical College, and at one time United States Minister to Italy.

[16] On June 6, 1910, The Samuel D. Gross Professorship of Surgery was endowed at Jefferson Medical College by his daughter, Mrs. Maria Gross Horwitz, who gave $60,000 for the purpose. Dr. J. Chalmers Da Costa was appointed to the chair.

America has been slow to honor her illustrious dead of the medical profession. Of the fifty-one names in the Hall of Fame, New York University, only one—that of Dr. Oliver Wendell Holmes, is the name of a physician. But Dr. Holmes's name is there, not because of his distinguished professional ability; not because he coined the word "anaesthesia"; not because he was the first to recognize the contagiousness of puerperal fever, but by reason of his eminent literary genius.

Be this as it may, the great surgeon whose name and fame constitute the theme of this evening's meeting was not destined to go down to his grave "unwept, unhonored, and unsung." In the city of Washington, D. C., under the very dome of the capitol of one of the mightiest nations on the face of the globe, there stands a fitting monument to him, in enduring bronze. A loving medical profession presented the statue, which is of heroic size, and the Congress of the United States appropriated $1500 for the pedestal. The Gross statue was unveiled May 5, 1897. Dr. W. W. Keen, one of the eight great surgeons of the world, was the orator of the day. The statue bears the following inscription:

SAMUEL D. GROSS.

American physicians have erected
this statue to commemorate the great deeds
of a man who made such an impress
upon American surgery that it has served
to dignify American medicine.
1897.

Dr. Gross's name is one of the great names in American medicine and surgery that appear in mosaic in the ceiling of the Congressional Library at Washington.

Full of honors as of years, Dr. Gross sunk to his rest. Great as a medical teacher and investigator, greater still as a courageous and successful operator, greatest of all as a man and citizen, he left an impress upon his age and times which will probably never again be duplicated by any one man.

He is one of the few whose deeds live after them. Such as he have been characterized by a gifted poetess as being of

The immortal dead who live again
In minds made better by their presence.

Dead? No! my dear hearers. Such a name is not "born to die." Samuel David Gross, "America's foremost surgeon," *is not dead*. True enough, he has passed from the sphere of action; he has rested from his arduous labors these twenty-seven years; but "his works do follow him." He still lives in the surgical principles which he so ably advocated; and in the hearts of those of us who cherish the traditions of our time-honored profession and believe, with the people of Kentucky, that a fitting attribute of a truly great physician or surgeon is the one implied by the inscription: "The milk-white flower of a stainless life."

NOTES AND NEWS.

MEDICAL EXAMINATIONS.

TREASURY DEPARTMENT.

BUREAU OF PUBLIC HEALTH AND MARINE-HOSPITAL SERVICE.
WASHINGTON, January 30, 1912.

A board of commissioned medical officers will be convened to meet at the Bureau of Public Health and Marine-Hospital Service, 3 B Street, S. E., Washington, D. C., Monday, April 8, 1812, at 10 o'clock a. m., for the purpose of examining candidates for admission to the grade of assistant surgeon in the Public Health and Marine-Hospital Service.

Candidates must be between 22 and 30 years of age, graduates of a reputable medical college, and must furnish testimonials from responsible persons as to their professional and moral character.

The following is the usual order of the examinations: 1, physical; 2, oral; 3, written; 4, clinical.

In addition to the physical examination, candidates are required to certify that they believe themselves free from any ailment which would disqualify them for service in any climate.

The examinations are chiefly in writing, and begin with a short autobiography of the candidate. The remainder of the written exercise consists in examination of the various branches of medicine, surgery, and hygiene.

The oral examination includes subjects of preliminary education, history, literature, and natural sciences.

The clinical examination is conducted at a hospital, and when practicable, candidates are required to perform surgical operations on a cadaver.

Successful candidates will be numbered according to their attainments on examination, and will be commissioned in the same order as vacancies occur.

Upon appointment the young officers are, as a rule, first assigned to duty at one of the large hospitals, as at Boston, New York, New Orleans, Chicago, or San Francisco.

After four years' service, assistant surgeons are entitled to examination for promotion to the grade of passed assistant surgeon.

Promotion to the grade of surgeon is made according to seniority and after due examination, as vacancies occur in that grade.

Assistant surgeons receive $1600, passed assistant surgeons $2000, and surgeons $2500, a year. When quarters are not provided, commutation at the rate of $30, $40, and $50 a month, according to grade, is allowed.

All grades above that of assistant surgeon receive longevity pay, 10 per cent in addition to the regular salary for every five years' service up to 40 per cent. after twenty years' service.

The tenure of office is permanent. Officers traveling under orders are allowed actual expenses.

For further information, or for invitation to appear before the board of examiners, address "Surgeon-General, Public Health and Marine-Hospital Service, Washington, D. C."

THE JOHNS HOPKINS HOSPITAL BULLETIN.

It is issued monthly. Volume XXIII is now in progress. The subscription price is $2.00 per year. (Foreign postage, 50 cents.) Price of cloth-bound volumes, $2.50 each.

A complete index to Vols. I-XVI of the Bulletin has been issued. Price, 50 cents, bound in cloth.

Orders should be addressed to THE JOHNS HOPKINS PRESS, BALTIMORE, MD.

NOTES ON NEW BOOKS.

Further Researches into Induced Cell-Reproduction and Cancer. Consisting of papers by H. C. Ross, M. R. C. S., J. W. CROPPER, M. B., and C. H. Ross, M. R. C. S. With Illustrations. The McFadden Researches. (*London: John Murray; Philadelphia: P. Blakiston's Son & Co., 1911.*)

About a year ago, Dr. H. C. Ross wrote a book entitled "Induced Cell-Reproduction and Cancer." The sale of this work, it is said, was interfered with, more or less, by a disagreeable quarrel between the author and a committee of his scientific friends who had been selected to support and advise him in his work. These "Further Researches" are sent out with a typewritten letter by his brother, Sir Ronald Ross, which we fear will not help the sale of the work. The quarrel is not of the least importance, and we do not care to hear only one side of it, and when Sir Ronald Ross says that "Scientific men in America should know that the work is not only sound, but, in my opinion, contains a discovery of very high importance," he is casting a slur on our scientists. They do not require Sir Ronald Ross's endorsement of his brother's work upon which to found their own judgment of the work, nor are they so narrow-minded as to be led astray by a quarrel about which many of them have never heard. The less said about the quarrel the better. The original work and this supplement will be judged on their merits, and there is no fear that Dr. Ross's discoveries will be overlooked if they are important, for there is no international clique attempting to suppress his work.

A Handbook of the Diseases of the Eye and their Treatment. By SIR HENRY R. SWANZY, M. D., etc., and LOUIS WERNER, M. B., etc. Tenth Edition. With Illustrations. $4.00. (*Philadelphia: P. Blakiston's Son & Co., 1912.*)

Careful revision of this well-known work keeps it a much valued book by students and practitioners. This edition for the first time contains some colored illustrations by Dr. Werner, which will add to its popularity. As produced by the publishers it is an attractive manual in its new form and size.

Microbiology for Agricultural and Domestic Science Students. Edited by CHARLES E. MARSHALL, Professor of Bacteriology and Hygiene, Michigan Agricultural College. $2.50. (*Philadelphia: P. Blakiston's Son & Co., 1911.*)

This text-book, as stated in its title, is intended primarily for students of agriculture and domestic science, and aims "to provide the fundamental and guiding principles of the subject, and to show just how these principles fit into the subjects of a more or less strictly professional or practical nature." At least for the two special branches mentioned it has been as well done as could be expected in a course not necessarily accompanied by practical laboratory exercises. The numerous contributors have for the most part handled their subjects well, and there is neither a conspicuous lack of unity nor much unnecessary repetition. The morphology and physiology of micro-organisms receive treatment that is adequate for the purposes of the book; while the practical applications to air, water, soil, foods, and dairy products are also very good.

The division treating of microbial diseases of man and animals is hardly adequate for the needs of medical students; however, the authors have compressed most of the essential facts into a very small compass. The section on "Immunity and Susceptibility" is marred by several serious inaccuracies. For example (page 562), the writer refers the well-known complement fixation test of Bordet and Gengou to Neisser and Wechsberg, tending to confuse with it the "complement deviation" phenomenon of the latter authors. Further, in the confused description of Wright's method of determining the opsonic index (page 566), the differences between normal and diseased individuals are referred incorrectly to differences in their leucocytes, instead of to differences in their serum.

Aside from this, the book is to be commended, and should aid in extending the practical application of knowledge gained in the laboratory to the industries in question. P. W. C.

Fourth Scientific Report on the Investigations of The Imperial Cancer Research Fund. Under the direction of the Royal College of Physicians in London and the Royal College of Surgeons of England. By DR. E. F. BASHFORD, General Superintendent of Research and Director of the Laboratory. Published by the Authority of the Executive Committee. 7/6. (*London: Taylor and Francis, 1911.*)

This long and admirable report is made up of three papers as follows: 1, Spontaneous Tumors in Mice, by Dr. Haaland; 2, Cancerous Ancestry and the Incidence of Cancer in Mice, by Dr. Murray; and 3, The Behavior of Tumor-Cells during Propagation, by Dr. Bashford, the Director. The first and third papers comprise most of the volume, as Dr. Murray's is but brief, though important, as it deals with the heredity of tumors in many generations of mice. This question of heredity is one of fundamental interest to all students of cancer problems, and though the data derived from animals cannot be applied directly to human beings, yet each study of this nature helps to throw some light on a very obscure point. Dr. Bashford's introduction gives to those unprepared, by lack of sufficiently detailed knowledge, to read through the report, a most illuminating résumé of the advance made in the study of many factors of this disease in the last few years. No thorough student of cancer can afford not to be at least acquainted with the findings of this Research Fund.

Oxford Medical Publications: Tuberculous Diseases of Bones and Joints. Their Pathology, Symptoms and Treatment. By SIR W. WATSON CHEYNE, Bart., etc. Second Edition. $5.50. (*London: Henry Frowde, and Hodder & Stoughton, 1911.*)

The true student of surgery, the specialist, will find this a most interesting work, as it represents the views of a man who has lived long enough to watch the changes that have taken place in the minds of surgeons as to the correct methods of handling these diseases, and who here expresses his own opinions after careful thought on the matter, and this author's opinions, as surgeons know, are deserving of the highest consideration. The illustrations are well chosen and sufficient in number, and the book, as a whole, is a sample of the excellent product of the Oxford University Press.

Electricity: Its Medical and Surgical Applications, Including Radiotherapy and Phototherapy. By CHARLES S. POTTS, M. D. Illustrated. (*Philadelphia and New York: Lea & Febiger, 1911.*)

This book is divided into seven sections: 1, Electricity; 2, Electrophysiology; 3, Electrodiagnosis and Electroprognosis; 4, General Electrotherapeutics; 5, Methods of obtaining general and local effects by the indirect action of electricity; 6, Special Electrotherapeutics; and 7, The Application of the Röntgen rays in medicine, thus making a volume of nearly 500 pages of text. There is also a good index. The author's arrangement of his material is a more fortunate one than that usually employed by writers on this branch of medicine. As he says in his preface, "The custom, hitherto, has been to consider the physiological action, therapeutic uses, and methods of application of each form of current separately. In this volume, on the contrary, these subjects have been discussed collectively, according to a medical.

rather than a physical subdivision. In other words, instead of devoting one section exclusively to the constant current, another to the static current, and so on, the author has grouped these modalities according to the effects produced." This method of arrangement will certainly appeal to students, and the entire book strikes us as one that both doctors and students will find helpful and well adapted to their needs. In this work, Dr. Potts has been assisted by Drs. H. C. Richards and H. K. Pancoast, who have respectively written the chapters on Electrophysics and Röntgen Rays.

Meine Präparationsmethode des Operationsfeldes mittels Jodtinktur. Von Kgl. Rat. Dr. Antonio Grossich. 75 cents. (*Berlin und Wien: Urban & Schwarzenberg; New York: Rebman Company, 1911.*)

Doctors, who can read German, will find this small work useful. Dr. Grossich presents a brief report on his own observations, and the possibly harmful effects of the tincture of iodine, and republishes three articles by himself on this subject, and gives an abstract of papers and personal communications by others who have tried this method of skin disinfection. The author's conclusions are: 1, that his method of preparation in the treatment of accidental injuries accomplishes a great deal, and to use a colloquialism, "cannot be beaten"; 2, that in urgent cases it is quite irreplaceable; and 3, that in aseptic operations it offers the best method. The value of the tincture of iodine as a means of disinfecting the skin cannot be seriously questioned, but we feel that Dr. Grossich goes too far in his commendation, when, to support his ideas, he states that bacteria pass through invisible holes in rubber gloves during the course of an operation. This may occur, but the danger of a wound being infected in this way need not really be considered for a moment. Dr. Grossich thus tries to prove that all infections of wounds occurring after the use of iodine are due to some other cause than the inefficacy of the iodine itself. This is exaggerated, but none the less his essay is well worth study.

The Diagnosis of Nervous Diseases. By Purves Stewart, M. A., M. D., Edin., F. R. C. P., etc. Third Edition. Revised and Enlarged. (*London: Edward Arnold; New York: E. B. Treat & Co., 1911.*)

Except by the specialist, this book has not received the attention it deserves in this country. It has already been translated into French and German, and for the beginner is especially useful, as "it approaches the subject of diagnosis of nervous diseases from the clinical standpoint, avoiding abstruse details of purely theoretical interest." This point of view should make it especially welcome to the student and general practitioner.

Diseases of the Digestive Canal (Œsophagus, Stomach, Intestines). By Dr. Paul Cohnheim, Berlin. From the Second German Edition. Edited and Translated by Dudley Fulton, M. D., etc. Illustrated. Second Edition. (*Philadelphia and London: J. B. Lippincott Company.*)

To physicians who do not know this book, we commend it. This group of diseases is ever a stumbling-block to the general practitioner, and from the clear exposition of them, as given by Dr. Cohnheim, he can gain much assistance. It is encouraging to note that the second German edition has been so promptly translated.

Swamp Fever in Horses. By L. Van Es, E. D. Harris, and A. F. Schalk. Bulletin 94. (*Fargo: N. D., September, 1911.*)

The North Dakota Agricultural Experiment Station has just published this report from its Department of Veterinary Science. It is an important contribution to the already large literature on a disease of horses about which little is definitely and accurately known, except that to farmers it is a question of grave importance in certain parts of the country, since the mortality among the horses affected is high. Veterinary students will be glad to have this new report, which, though it contains little that is new on the subject, deals with the disease in a satisfactory way, and helps to add a little light on some of the obscure points.

Manual of Operative Surgery. By John Fairbairn Binnie, A. M., C. M. (Aberdeen), etc. Fifth Edition. Revised and Enlarged. With 1365 Illustrations. $7.00. (*Philadelphia: P. Blakiston's Son & Co., 1911.*)

The two volumes, which made up this book when it last appeared, are now combined into one, not too large, also well printed and abundantly illustrated. In its new form it will doubtless be still more acceptable to the profession. Many of the illustrations are purely diagrammatic, and in this form are perhaps more readily understood by the student, though they do not commend themselves artistically. But this is a side-issue, and Dr. Binnie's manual is good.

Text-Book of Medical Jurisprudence and Toxicology. By John J. Reese, M. D., etc. Eighth Edition. Revised by D. J. McCarthy, M. D., etc. $3.00. (*Philadelphia: P. Blakiston's Son & Co., 1911.*)

To this well-known work the editor has merely added a few new sections on the commitment of the insane, anaphylaxis, formaldehyde and chronic bismuth poisoning. He has also revised the chapter on insanity. Thus this text-book still remains largely the work of the author, and will continue to be welcome to a large body of students.

Progressive Medicine. Vol. IV. December, 1911. Edited by Hobart Amory Hare, M. D., etc., assisted by Leighton F. Appleman, M. D., etc. (*Philadelphia and New York: Lea & Febiger, 1911.*)

This volume includes a review of recent papers in Diseases of the Digestive Tract and Allied Organs, The Liver, Pancreas and Peritoneum by Lavenson, Diseases of the Kidneys by Bradford, Genito-Urinary Diseases by Bonney, Surgery of the Extremities, Shock, Anæsthesia, Infections, Fractures and Dislocations, and Tumors by Bloodgood, and Practical Therapeutic Referendum by Landis, with an Index. The value of this work is in the presentation by specialists, who are cognizant of all the work that is being done along these lines, of the best opinion on these conditions as expressed in the current literature. Progressive Medicine is a most useful reference book for the general practitioner.

Through Rebman Company (New York) can be secured, free of charge, a well arranged catalogue of the post-graduate medical work at the University of Vienna, prepared by the publishers, Urban & Schwarzenberg (Berlin & Vienna). This gives a list of the teachers, of the courses and lectures and places where they are given, and is printed in English, French and German, side by side, so as to be most convenient and useful for any student or doctor thinking of going to Vienna to pursue his medical studies.

P. Blakiston's Son & Co., of Philadelphia, have published their annual Physician's Visiting List for 1912. It is a vest-pocket memorandum book with its serviceable tables of dosage, poisons and their antidotes, etc., which many a practitioner will find useful.

The Johns Hopkins Hospital Bulletins are issued monthly. They are printed by the LORD BALTIMORE PRESS, Baltimore. Subscriptions, $2.00 a year (foreign postage, 50 cents), may be addressed to the publishers, THE JOHNS HOPKINS PRESS, BALTIMORE; single copies will be sent by mail for twenty-five cents each. Single copies may also be procured from the BALTIMORE NEWS CO., Baltimore.